BETA LACTAM COMPOUNDS AND THEIR USE AS INHIBITORS OF TRYPTASE

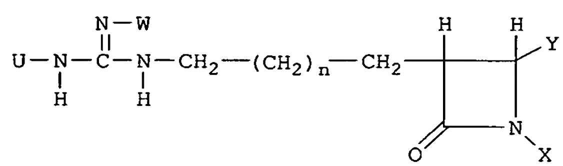
This application claims the priority benefit of U.S. Provisional Application No. 60/434,060 filed December 17, 2002, the disclosure of which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to beta lactam compounds which are inhibitors of tryptase and to a method for preventing or treating asthma and chronic rhinitis employing such compounds.

BACKGROUND OF THE INVENTION

Han in U.S. Patents Nos. 5,037,819, 5,110,812, 5,175,283, 5,250,677 and 5,326,863 discloses 3-guanidinoalkyl-2-azetidinones of the formula

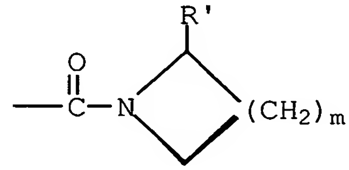


wherein:

U and W are independently selected from hydrogen and amino protecting groups;

n is an integer from 1 to 3;

X is hydrogen, trialkylsilyl, arylsulfonyl, amino substituted arylsulfonyl, alkylsulfonyl, arylaminocarbonyl, alkylcarbonyl or arylcarbonyl;

Y is hydrogen, arylalkenyl, arylalkyl, formyl, carboxy, alkoxycarbonyl, acyloxy, arylthio, arylsulfinyl, arylsulfonyl, alkythio, alkylsulfinyl, alkylsulfonyl, arylaminocarbonyl, $-C(=O)-NH-CH_2-C(=O)-OR$, or  ;

R is hydrogen, alkyl, or arylalkyl;

m is an integer from 1 to 3; and

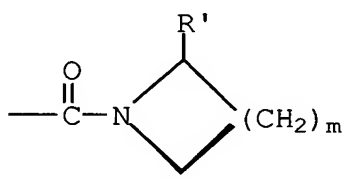
R′ is hydrogen or -CO_2R″ wherein R″ is hydrogen, alkyl, or arylalkyl.

Han further discloses that the above compounds wherein:

U and W are hydrogen;

X is arylsulfonyl, amino substituted arylsulfonyl, alkylsulfonyl, arylaminocarbonyl, alkylcarbonyl, or arylcarbonyl; and

Y is hydrogen, arylalkyl, carboxy, alkoxycarbonyl, acyloxy, arylsulfonyl, alkylthio, alkylsulfonyl, arylaminocarbonyl, $-C(=O)-NH-CH_2-C(=O)-OR$, or

 ;

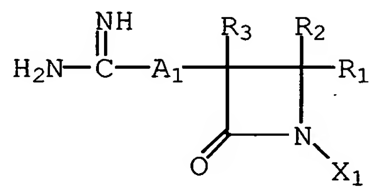
R is hydrogen, alkyl or arylalkyl;

R′ is hydrogen or -CO_2R″;

R″ is hydrogen, alkyl, or arylalkyl and pharmaceutically acceptable salts thereof are inhibitors against serine proteases, particularly against thrombin and trypsin, and can be used to control blood coagulation or to treat pancreatitis.

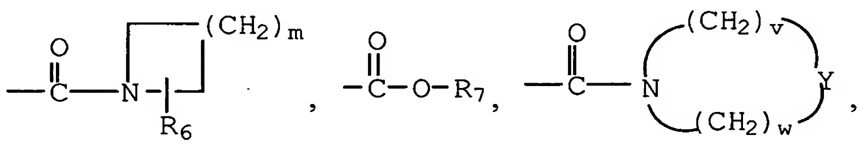
Han defines "aryl" as a phenyl or naphthyl group which may be unsubstituted or substituted with one or more groups such as amino, nitro, or alkyl and defines "amino" as unsubstituted or substituted with one or two alkyl radicals.

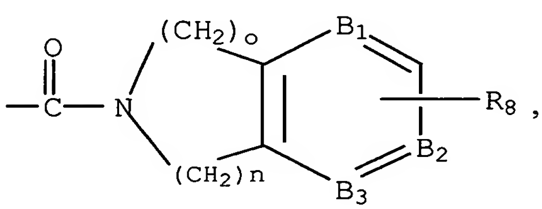
U.S. Patents Nos. 6,335,324 to Bisacchi et al. discloses compounds of the following formula:



wherein:

R_1 is hydrogen, carboxy, alkoxycarbonyl, A_2-aryl, $-\overset{O}{\overset{\|}{C}}-R_7$,



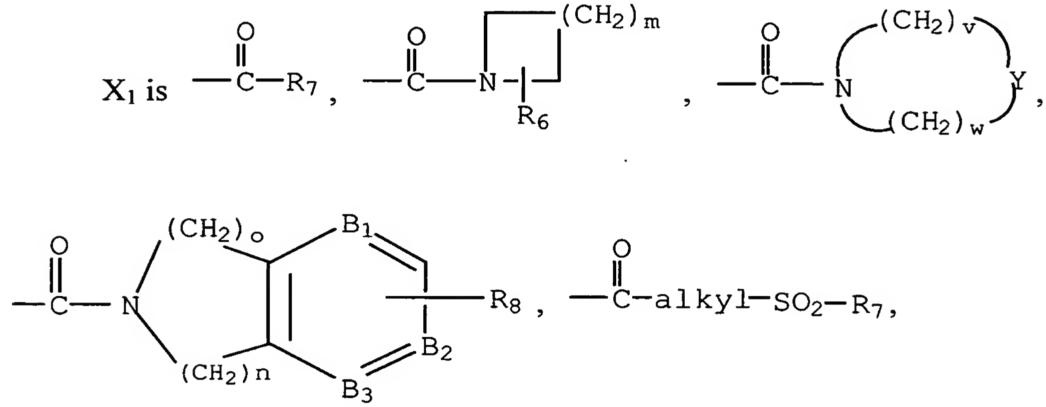
 , $-\overset{O}{\overset{\|}{C}}-CH_2-O-R_{10}$, $-SO_2-R_7$,

$-\overset{O}{\overset{\|}{C}}-\underset{R_9}{N}-A_2-\underset{R_9}{N}-\overset{O}{\overset{\|}{C}}-R_4$, $-\overset{O}{\overset{\|}{C}}-\underset{R_9}{N}-A_2-\underset{R_9}{N}-\overset{O}{\overset{\|}{C}}-OR_4$, $-\overset{O}{\overset{\|}{C}}-alkyl-SO_2-R_7$, or

$-C(=O)-aryl-SO_2-R_7$, or R_1 is alkyl provided that R_2 is alkyl and R_3 is hydrogen;

R_2 and R_3 are both hydrogen, or R_2 is alkyl provided that R_3 is hydrogen, or R_3 is alkyl provided that R_2 is hydrogen;

X_1 is

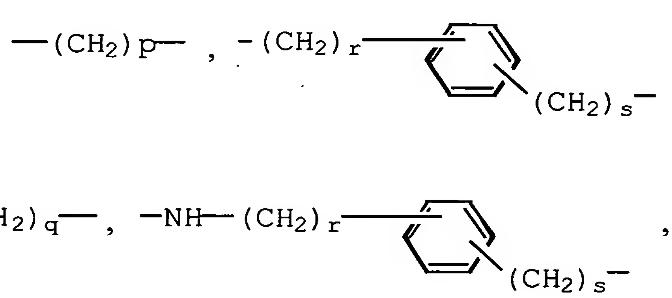


$-C(=O)-aryl-SO_2-R_7$, $-C(=O)-CH_2-O-R_{10}$, $-SO_2-R_7$,

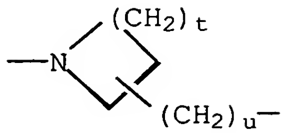
$-C(=O)-NH-SO_2-R_7$, $-C(=O)-N(R_9)-A_2-N(R_9)-C(=O)-R_4$, or

$-C(=O)-N(R_9)-A_2-N(R_9)-C(=O)-OR_4$;

A_1 is

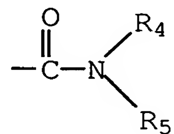
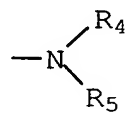


, or

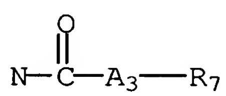
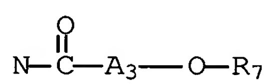
 ;

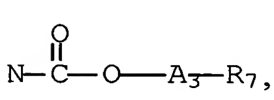
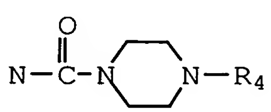
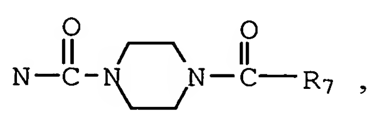
R_4 and R_5 are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, A_2-aryl-A_3-heterocycloalkyl, aryl-A_3-substituted aryl, A_2-aryl-A_3-substitued aryl, aryl-A_3-substituted cycloalkyl, A_2-aryl-A_3-substituted cycloalkyl, cycloalkyl- A_3-cycloalkyl, A_2-cycloalkyl-A_3-cycloalkyl, cycloalkyl-A_3-aryl, A_2-cycloalkyl-A_3-aryl, cycloalkyl-A_3-heteroaryl, A_2-cycloalkyl-A_3-heteroaryl, cycloalkyl-A_3-heterocycloalkyl, A_2-cycloalkyl-A_3-heterocycloalkyl, cycloalkyl-A_3-substituted cycloalkyl, A_2-cycloalkyl-A_3-substituted cycloalkyl, cycloalkyl-A_3-substituted aryl, A_2-cycloalkyl-A_3-substituted aryl, substituted cycloalkyl-A_3-cycloalkyl, A_2-substituted cycloalkyl-A_3-cycloalkyl, substituted cycloalkyl-A_3-substituted cycloalkyl, A_2-substituted cycloalkyl-A_3-substituted cycloalkyl, substituted cycloalkyl-A_3-aryl, A_2-substituted cycloalkyl-A_3-aryl, substituted cycloalkyl-A_3-heteroaryl, A_2-substituted cycloalkyl-A_3-heteroaryl, substituted cycloalkyl-A_3-heterocycloalkyl, A_2-substituted cycloalkyl-A_3-heterocycloalkyl, substituted cycloalkyl-A_3-substituted aryl, A_2-substituted cycloalkyl-A_3-substituted aryl, heteroaryl-A_3-heteroaryl, A_2-heteroaryl-A_3-heteroaryl, heteroaryl-A_3-cycloalkyl, A_2-heteroaryl-A_3-cycloalkyl, heteroaryl-A_3-substituted cycloalkyl, A_2-heteroaryl-A_3-substituted cycloalkyl, heteroaryl-A_3-aryl, A_2-heteroaryl-A_3-aryl, heteroaryl-A_3-heterocycloalkyl, A_2-heteroaryl-A_3-heterocycloalkyl, heteroaryl-A_3-substituted aryl, A_2-heteroaryl-A_3-substituted aryl, heterocycloalkyl-A_3-heterocycloalkyl, A_2-heterocycloalkyl-A_3-heterocycloalkyl, heterocycloalkyl-A_3-cycloalkyl, A_2-heterocycloalkyl-A_3-cycloalkyl, heterocycloalkyl-A_3-substituted cycloalkyl, A_2-heterocycloalkyl-A_3-substituted cycloalkyl, heterocycloalkyl-A_3-aryl, A_2-heterocycloalkyl-A_3-aryl, heterocycloalkyl-A_3-substituted aryl, A_2-heterocycloalkyl-A_3-substituted aryl, heterocycloalkyl-A_3-heteroaryl, A_2-heterocycloalkyl-A_3-heteroaryl, substituted aryl-A_3-substituted aryl,

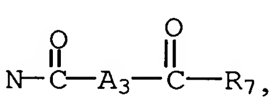
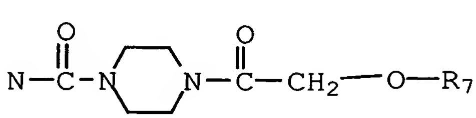
A_2-substituted aryl-A_3-substituted aryl, substituted aryl-A_3-cycloalkyl, A_2-substituted aryl-A_3-cycloalkyl, substituted aryl-A_3-substituted cycloalkyl, A_2-substituted aryl-A_3-substituted cycloalkyl, substituted aryl-A_3-aryl, A_2-substituted aryl-A_3-aryl, substituted aryl-A_3-heteroaryl, A_2-substituted aryl-A_3-heteroaryl, substituted aryl-A_3-heterocycloalkyl, and A_2-substituted aryl-A_3-heterocycloalkyl;

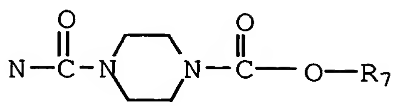
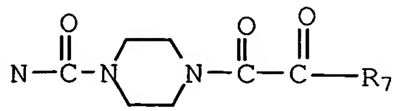
R_6 is hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, A_2-aryl-A_3-heterocycloalkyl, carboxy, alkoxycarbonyl, aryloxycarbonyl,  ,  , alkoxycarbonylamino, aryloxycarbonylamino, arylcarbonylamino, -N(alkyl)(alkoxycarbonyl), -N(alkyl)(aryloxycarbonyl), alkylcarbonylamino, -N(alkyl)(alkylcarbonyl), or -N(alkyl)(arylcarbonyl);

m is an integer from 1 to 5;

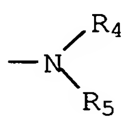
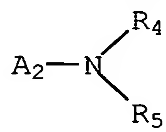
Y is O, S, N-R_4, N-SO_2-R_7,  ,  ,

 ,  ,  ,

 ,  ,

 , or  ;

R_7 is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, A_2-aryl-A_3-heterocycloalkyl, aryl-A_3-substituted aryl, A_2-aryl-A_3-substitued aryl, aryl-A_3-substituted cycloalkyl, A_2-aryl-A_3-substituted cycloalkyl, cycloalkyl- A_3-cycloalkyl, A_2-cycloalkyl-A_3-cycloalkyl, cycloalkyl-A_3-aryl, A_2-cycloalkyl-A_3-aryl, cycloalkyl-A_3-heteroaryl, A_2-cycloalkyl-A_3-heteroaryl, cycloalkyl-A_3-heterocycloalkyl, A_2-cycloalkyl-A_3-heterocycloalkyl, cycloalkyl-A_3-substituted cycloalkyl, A_2-cycloalkyl-A_3-substituted cycloalkyl, cycloalkyl-A_3-substituted aryl, A_2-cycloalkyl-A_3-substituted aryl, substituted cycloalkyl-A_3-cycloalkyl, A_2-substituted cycloalkyl-A_3-cycloalkyl, substituted cycloalkyl-A_3-substituted cycloalkyl, A_2-substituted cycloalkyl-A_3-substituted cycloalkyl, substituted cycloalkyl-A_3-aryl, A_2-substituted cycloalkyl-A_3-aryl, substituted cycloalkyl-A_3-heteroaryl, A_2-substituted cycloalkyl-A_3-heteroaryl, substituted cycloalkyl-A_3-heterocycloalkyl, A_2-substituted cycloalkyl-A_3-heterocycloalkyl, substituted cycloalkyl-A_3-substituted aryl, A_2-substituted cycloalkyl-A_3-substituted aryl, heteroaryl-A_3-heteroaryl, A_2-heteroaryl-A_3-heteroaryl, heteroaryl-A_3-cycloalkyl, A_2-heteroaryl-A_3-cycloalkyl, heteroaryl-A_3-substituted cycloalkyl, A_2-heteroaryl-A_3-substituted cycloalkyl, heteroaryl-A_3-aryl, A_2-heteroaryl-A_3-aryl, heteroaryl-A_3-heterocycloalkyl, A_2-heteroaryl-A_3-heterocycloalkyl, heteroaryl-A_3-substituted aryl, A_2-heteroaryl-A_3-substituted aryl, heterocycloalkyl-A_3-heterocycloalkyl, A_2-heterocycloalkyl-A_3-heterocycloalkyl, heterocycloalkyl-A_3-cycloalkyl, A_2-heterocycloalkyl-A_3-cycloalkyl, heterocycloalkyl-A_3-substituted cycloalkyl, A_2-heterocycloalkyl-A_3-substituted cycloalkyl, heterocycloalkyl-A_3-aryl, A_2-heterocycloalkyl-A_3-aryl, heterocycloalkyl-A_3-substituted aryl, A_2-heterocycloalkyl-A_3-substituted aryl, heterocycloalkyl-A_3-heteroaryl, A_2-heterocycloalkyl-A_3-heteroaryl, substituted aryl-A_3-substituted aryl, A_2-substituted aryl-A_3-substituted aryl,

substituted aryl-A_3-cycloalkyl, A_2-substituted aryl-A_3-cycloalkyl, substituted aryl-A_3-substituted cycloalkyl, A_2-substituted aryl-A_3-substituted cycloalkyl, substituted aryl-A_3-aryl, A_2-substituted aryl-A_3-aryl, substituted aryl-A_3-heteroaryl, A_2-substituted aryl-A_3-heteroaryl, substituted aryl-A_3-heterocycloalkyl, A_2-substituted aryl-A_3-heterocycloalkyl,  ,  ;

n and o are one or two provided that the sum of n plus o is two or three;

v and w are one, two, or three provided that the sum of v plus w is three, four, or five;

R_8 is hydrogen, halo, amino, -NH(lower alkyl), -N(lower alkyl)$_2$, nitro, alkyl, substituted alkyl, alkoxy, hydroxy, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, or A_2-aryl-A_3-heterocycloalkyl;

B_1, B_2 and B_3 are each CH, or two of B_1, B_2 and B_3 are CH and the other is N, or one of B_1, B_2 and B_3 is CH and the other two are N;

R_9 is hydrogen or lower alkyl;

R_{10} is alkyl, substituted alkyl, alkyl-O-alkyl, alkyl-O-alkyl-O-alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl or A_2-aryl-A_3-heterocyloalkyl;

R_{20} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, A_2-aryl, or A_2-substituted aryl;

R_{21} and R_{22} are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, A_2-aryl, and A_2-substituted aryl;

p is an integer from 2 to 6;

q is an integer from 1 to 6;

r is zero, 1 or 2;

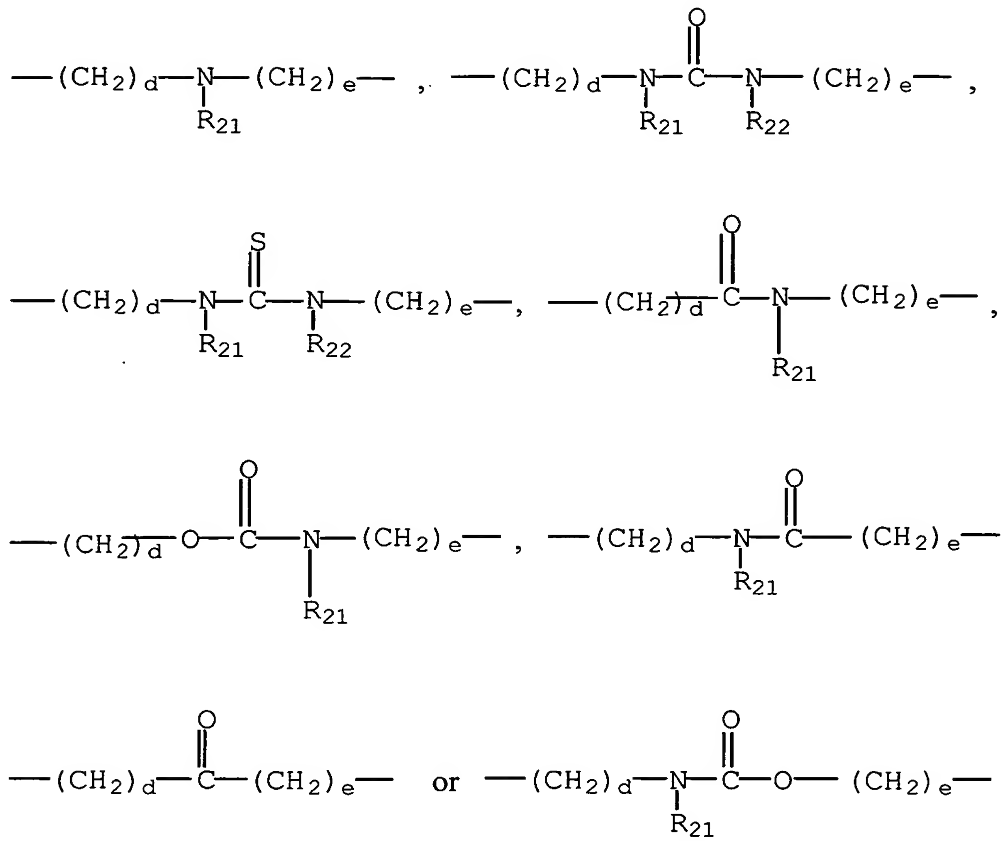
s is 1 or 2;

t is 1, 2, 3 or 4;

u is 1, 2 or 3;

A_2 is an alkylene or a substituted alkylene bridge of 1 to 10 carbons, an alkenyl or substituted alkenyl bridge of 2 to 10 carbons having one or more double bonds, or an alkynyl or substituted alkynyl bridge of 2 to 10 carbons having one or more triple bonds;

A_3 is a bond, an alkylene or a substituted alkylene bridge of 1 to 10 carbons, an alkenyl or substituted alkenyl bridge of 2 to 10 carbons having one or more double bonds, an alkynyl or substituted alkynyl bridge of 2 to 10 carbons having one or more triple bonds, $-(CH_2)_d-O-(CH_2)_e-$, $-(CH_2)_d-S-(CH_2)_e-$,



; and

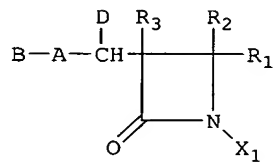
d and e are independently selected from zero and an integer from 1 to 10 provided that the sum of d plus e is no greater than 10.

SUMMARY OF THE INVENTION

This invention is directed to the novel beta lactam compounds of formula I shown below and to a method for the use of such compounds as inhibitors of various *in vivo* enzyme systems including tryptase, thrombin, trypsin, Factor Xa, Factor VIIa, and urokinase-type plasminogen activator and their use in treating and/or preventing asthma and/or allergic rhinitis.

Compounds of this invention have the formula:

I.



wherein

D is H or OR^a;

R^a is H or alkyl;

A is a linear string of A^1, A^2, A^3, A^4, A^5, A^6, A^7 and/or A^8, in any order, such that A^1 may occur in the string from 0 to 6 times;

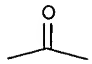
A^2 may occur in the string from 0 to 2 times;

A^3, A^4, A^5, A^6, A^7 and/or A^8 may each occur in the string 0 or 1 time, such that the total number of linear A groups is 0 to 6;

A^1 is $-\overset{R_{5a}{}^{1}}{\underset{R_{5a}}{\overset{|}{\underset{|}{C}}}}-$;

A^2 is $-\overset{R_{5b}}{\overset{|}{(C}}{=}\overset{R_{5c}}{\overset{|}{C)}}-$;

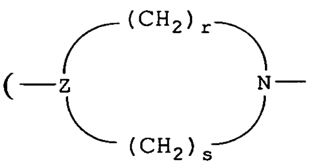
A^3 is $-\underset{R_{5d}}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-$, -cycloheteroalkyl$-\overset{O}{\overset{\|}{C}}-$, or $-\overset{O}{\overset{\|}{C}}-$cycloheteroalkyl;

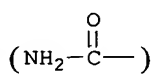
A^4 is ;

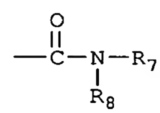
A^5 is cycloalkyl;

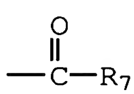
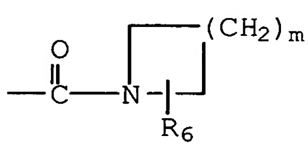
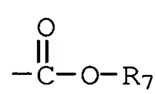
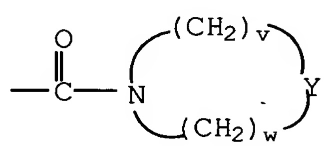
A^6 is aryl;

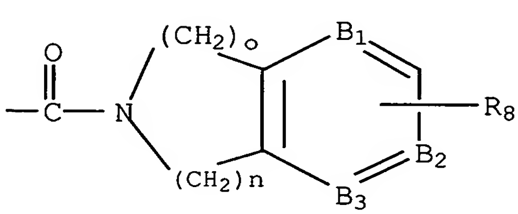
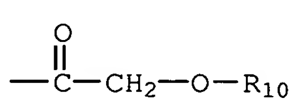
A^7 is heteroaryl;

A^8 is cycloheteroalkyl ( where Z is CH or N, r is 0 to 3 and s is 0 to 3) wherein R_{5a}, $R_{5a}{}^{1}$, R_{5b}, R_{5c}, and R_{5d} are the same or different and are H, alkyl, aryl, arylalkyl, halo or NO_2;

B is amino, aminoalkyl, amino cycloalkyl, cycloheteroalkyl, aryl, heteroaryl, alkylamino, carboxamido () or cycloalkyl;

R_1 is hydrogen, carboxy, alkoxycarbonyl, A_2-aryl, alkyl, ,

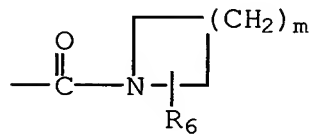
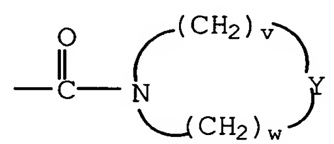
, , , ,

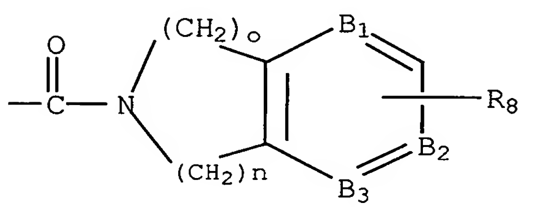
, , SO_2-R_7,

$-C(=O)-N(R_9)-A_2-N(R_9)-C(=O)-R_4$, $-C(=O)-N(R_9)-A_2-N(R_9)-C(=O)-OR_4$, $-C(=O)-\text{alkyl}-SO_2-R_7$, or

$-C(=O)-\text{aryl}-SO_2-R_7$;

R_2 and R_3 are the same or different and are independently hydrogen or alkyl;

X_1 is $-C(=O)-R_7$, , ,

, $-C(=O)-\text{alkyl}-SO_2-R_7$,

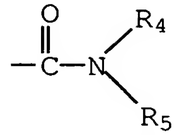
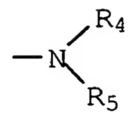
$-C(=O)-\text{aryl}-SO_2-R_7$, $-C(=O)-CH_2-O-R_{10}$, $-SO_2-R_7$,

$-C(=O)-NH-SO_2-R_7$, $-C(=O)-N(R_9)-A_2-N(R_9)-C(=O)-R_4$, or $-C(=O)-N(R_9)-A_2-N(R_9)-C(=O)-OR_4$;

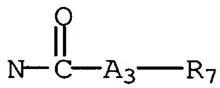
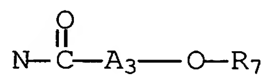
R_4 and R_5 are the same or different and are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, A_2-aryl-A_3-heterocycloalkyl, aryl-A_3-substituted aryl, A_2-aryl-A_3-substitued aryl, aryl-A_3-substituted cycloalkyl, A_2-aryl-A_3-substituted cycloalkyl, cycloalkyl- A_3-cycloalkyl, A_2-cycloalkyl-A_3-cycloalkyl, cycloalkyl-A_3-

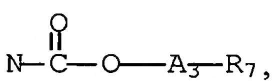
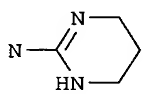
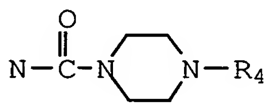
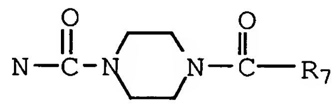
aryl, A_2-cycloalkyl-A_3-aryl, cycloalkyl-A_3-heteroaryl, A_2-cycloalkyl-A_3-heteroaryl, cycloalkyl-A_3-heterocycloalkyl, A_2-cycloalkyl-A_3-heterocycloalkyl, cycloalkyl-A_3-substituted cycloalkyl, A_2-cycloalkyl-A_3-substituted cycloalkyl, cycloalkyl-A_3-substituted aryl, A_2-cycloalkyl-A_3-substituted aryl, substituted cycloalkyl-A_3-cycloalkyl, A_2-substituted cycloalkyl-A_3-cycloalkyl, substituted cycloalkyl-A_3-substituted cycloalkyl, A_2-substituted cycloalkyl-A_3-substituted cycloalkyl, substituted cycloalkyl-A_3-aryl, A_2-substituted cycloalkyl-A_3-aryl, substituted cycloalkyl-A_3-heteroaryl, A_2-substituted cycloalkyl-A_3-heteroaryl, substituted cycloalkyl-A_3-heterocycloalkyl, A_2-substituted cycloalkyl-A_3-heterocycloalkyl, substituted cycloalkyl-A_3-substituted aryl, A_2-substituted cycloalkyl-A_3-substituted aryl, heteroaryl-A_3-heteroaryl, A_2-heteroaryl-A_3-heteroaryl, heteroaryl-A_3-cycloalkyl, A_2-heteroaryl-A_3-cycloalkyl, heteroaryl-A_3-substituted cycloalkyl, A_2-heteroaryl-A_3-substituted cycloalkyl, heteroaryl-A_3-aryl, A_2-heteroaryl-A_3-aryl, heteroaryl-A_3-heterocycloalkyl, A_2-heteroaryl-A_3-heterocycloalkyl, heteroaryl-A_3-substituted aryl, A_2-heteroaryl-A_3-substituted aryl, heterocycloalkyl-A_3-heterocycloalkyl, A_2-heterocycloalkyl-A_3-heterocycloalkyl, heterocycloalkyl-A_3-cycloalkyl, A_2-heterocycloalkyl-A_3-cycloalkyl, heterocycloalkyl-A_3-substituted cycloalkyl, A_2-heterocycloalkyl-A_3-substituted cycloalkyl, heterocycloalkyl-A_3-aryl, A_2-heterocycloalkyl-A_3-aryl, heterocycloalkyl-A_3-substituted aryl, A_2-heterocycloalkyl-A_3-substituted aryl, heterocycloalkyl-A_3-heteroaryl, A_2-heterocycloalkyl-A_3-heteroaryl, substituted aryl-A_3-substituted aryl, A_2-substituted aryl-A_3-substituted aryl, substituted aryl-A_3-cycloalkyl, A_2-substituted aryl-A_3-cycloalkyl, substituted aryl-A_3-substituted cycloalkyl, A_2-substituted aryl-A_3-substituted cycloalkyl, substituted aryl-A_3-aryl, A_2-substituted aryl-A_3-aryl, substituted aryl-A_3-heteroaryl, A_2-substituted aryl-A_3-heteroaryl, substituted aryl-A_3-heterocycloalkyl, and A_2-substituted aryl-A_3-heterocycloalkyl;

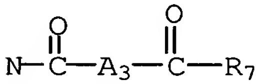
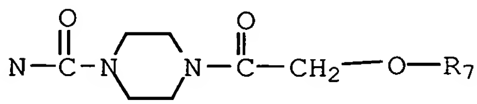
R_6 is hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, A_2-aryl-A_3-heterocycloalkyl, carboxy,

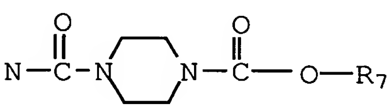
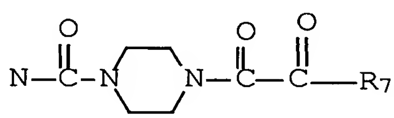
alkoxycarbonyl, aryloxycarbonyl, , , alkoxycarbonylamino, aryloxycarbonylamino, arylcarbonylamino, -N(alkyl)(alkoxycarbonyl), -N(alkyl)(aryloxycarbonyl), alkylcarbonylamino, -N(alkyl)(alkylcarbonyl), or -N(alkyl)(arylcarbonyl);

m is an integer from 1 to 5;

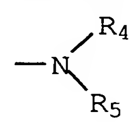
Y is O, S, N-R_4, N-SO_2-R_7, , ,

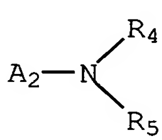
, , , ,

, ,

, or ;

R_7 is H, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, A_2-aryl-A_3-heterocycloalkyl, aryl-A_3-substituted aryl, A_2-aryl-A_3-substitued aryl, aryl-A_3-substituted cycloalkyl, A_2-aryl-A_3-substituted cycloalkyl, cycloalkyl- A_3-cycloalkyl, A_2-cycloalkyl-A_3-cycloalkyl, cycloalkyl-A_3-aryl, A_2-cycloalkyl-A_3-aryl, cycloalkyl-A_3-heteroaryl, A_2-cycloalkyl-A_3-heteroaryl, cycloalkyl-A_3-heterocycloalkyl, A_2-cycloalkyl-A_3-heterocycloalkyl,

cycloalkyl-A_3-substituted cycloalkyl, A_2-cycloalkyl-A_3-substituted cycloalkyl, cycloalkyl-A_3-substituted aryl, A_2-cycloalkyl-A_3-substituted aryl, substituted cycloalkyl-A_3-cycloalkyl, A_2-substituted cycloalkyl-A_3-cycloalkyl, substituted cycloalkyl-A_3-substituted cycloalkyl, A_2-substituted cycloalkyl-A_3-substituted cycloalkyl, substituted cycloalkyl-A_3-aryl, A_2-substituted cycloalkyl-A_3-aryl, substituted cycloalkyl-A_3-heteroaryl, A_2-substituted cycloalkyl-A_3-heteroaryl, substituted cycloalkyl-A_3-heterocycloalkyl, A_2-substituted cycloalkyl-A_3-heterocycloalkyl, substituted cycloalkyl-A_3-substituted aryl, A_2-substituted cycloalkyl-A_3-substituted aryl, heteroaryl-A_3-heteroaryl, A_2-heteroaryl-A_3-heteroaryl, heteroaryl-A_3-cycloalkyl, A_2-heteroaryl-A_3-cycloalkyl, heteroaryl-A_3-substituted cycloalkyl, A_2-heteroaryl-A_3-substituted cycloalkyl, heteroaryl-A_3-aryl, A_2-heteroaryl-A_3-aryl, heteroaryl-A_3-heterocycloalkyl, A_2-heteroaryl-A_3-heterocycloalkyl, heteroaryl-A_3-substituted aryl, A_2-heteroaryl-A_3-substituted aryl, heterocycloalkyl-A_3-heterocycloalkyl, A_2-heterocycloalkyl-A_3-heterocycloalkyl, heterocycloalkyl-A_3-cycloalkyl, A_2-heterocycloalkyl-A_3-cycloalkyl, heterocycloalkyl-A_3-substituted cycloalkyl, A_2-heterocycloalkyl-A_3-substituted cycloalkyl, heterocycloalkyl-A_3-aryl, A_2-heterocycloalkyl-A_3-aryl, heterocycloalkyl-A_3-substituted aryl, A_2-heterocycloalkyl-A_3-substituted aryl, heterocycloalkyl-A_3-heteroaryl, A_2-heterocycloalkyl-A_3-heteroaryl, substituted aryl-A_3-substituted aryl, A_2-substituted aryl-A_3-substituted aryl, substituted aryl-A_3-cycloalkyl, A_2-substituted aryl-A_3-cycloalkyl, substituted aryl-A_3-substituted cycloalkyl, A_2-substituted aryl-A_3-substituted cycloalkyl, substituted aryl-A_3-aryl, A_2-substituted aryl-A_3-aryl, substituted aryl-A_3-heteroaryl, A_2-substituted aryl-A_3-heteroaryl, substituted aryl-A_3-heterocycloalkyl, A_2-substituted aryl-A_3-heterocycloalkyl, , or

 ;

n and o are one or two provided that the sum of n plus o is two or three;

v and w are one, two, or three provided that the sum of v plus w is three, four, or five;

R_8 is hydrogen, halo, amino, -NH(lower alkyl), -N(lower alkyl)$_2$, nitro, alkyl, substituted alkyl, alkoxy, hydroxy, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl, or A_2-aryl-A_3-heterocycloalkyl;

B_1, B_2 and B_3 are each CH, or two of B_1, B_2 and B_3 are CH and the other is N, or one of B_1, B_2 and B_3 is CH and the other two are N;

R_9 is hydrogen or lower alkyl;

R_{10} is alkyl, substituted alkyl, alkyl-O-alkyl, alkyl-O-alkyl-O-alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, aryl, substituted aryl, A_2-aryl, A_2-substituted aryl, aryl-A_3-aryl, A_2-aryl-A_3-aryl, heteroaryl, A_2-heteroaryl, heterocycloalkyl, A_2-heterocycloalkyl, aryl-A_3-cycloalkyl, A_2-aryl-A_3-cycloalkyl, aryl-A_3-heteroaryl, A_2-aryl-A_3-heteroaryl, aryl-A_3-heterocycloalkyl or A_2-aryl-A_3-heterocycloalkyl;

R_{21} and R_{22} are the same or different and are independently selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, A_2-cycloalkyl, A_2-substituted cycloalkyl, A_2-aryl, and A_2-substituted aryl;

p is an integer from 2 to 6;

q is an integer from 1 to 6;

r is zero, 1, 2 or 3;

s is 1, 2 or 3;

t is 1, 2, 3 or 4;

u is 1, 2 or 3;

A_2 is an alkylene or a substituted alkylene bridge of 1 to 10 carbons, an alkenyl or substituted alkenyl bridge of 2 to 10 carbons having one or more double bonds, or an alkynyl or substituted alkynyl bridge of 2 to 10 carbons having one or more triple bonds;

A_3 is a bond, an alkylene or a substituted alkylene bridge of 1 to 10 carbons, an alkenyl or substituted alkenyl bridge of 2 to 10 carbons having one or more double bonds, an alkynyl or substituted alkynyl bridge of 2 to 10 carbons having one or more triple bonds; $-(CH_2)_d-O-(CH_2)_e-$, $-(CH_2)_d-S-(CH_2)_e-$,

$-(CH_2)_d-N(R_{21})-(CH_2)_e-$, $-(CH_2)_d-N(R_{21})-C(=O)-N(R_{22})-(CH_2)_e-$,

$-(CH_2)_d-N(R_{21})-C(=S)-N(R_{22})-(CH_2)_e-$, $-(CH_2)_d-C(=O)-N(R_{21})-(CH_2)_e-$,

$-(CH_2)_d-O-C(=O)-N(R_{21})-(CH_2)_e-$, $-(CH_2)_d-N(R_{21})-C(=O)-(CH_2)_e-$,

$$—(CH_2)_d—\overset{O}{\overset{\|}{C}}—(CH_2)_e— \quad \text{or} \quad —(CH_2)_d—\underset{R_{21}}{\underset{|}{N}}—\overset{O}{\overset{\|}{C}}—O—(CH_2)_e— ;$$

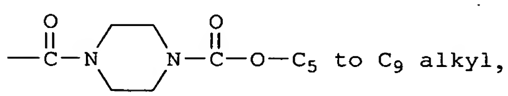
d and e are independently selected from zero and an integer from 1 to 10 provided that the sum of d plus e is no greater than 10;

and an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof, with the provisos that

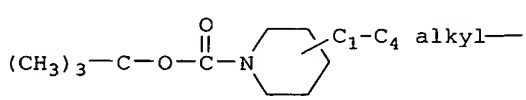
I. where R_1 is COOZ, where Z is $t—C_4H_9O\overset{O}{\overset{\|}{C}}—$ or $C_6H_5CH_2O\overset{O}{\overset{\|}{C}}—$, and $—A—\overset{D}{\overset{|}{C}}—$ is $(CH_2)_q$,

then B is other than amino or R_{20}-NH- where R_{20} is alkyl, cycloalkyl, A_2-cycloalkyl or A_2-aryl;

II. where R_1 is $C_6H_5CH_2O\overset{O}{\overset{\|}{C}}—$,

X_1 is , and

$—A—\overset{D}{\overset{|}{C}}—$ is other than

(1)  ,

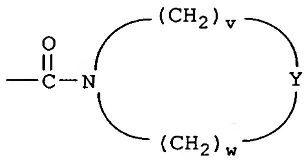
(2) $[(H_3C)_3—C—O—\overset{O}{\overset{\|}{C}}]_2—N—C_1\text{-}C_4 \text{ alkyl}—$,

(3) amino C_1-C_5 alkyl,

(4) C_1-C_4 alkylamino C_1-C_5 alkyl, or

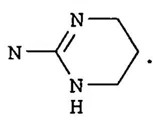
(5) piperidyl.

Preferred are compounds of formula I wherein

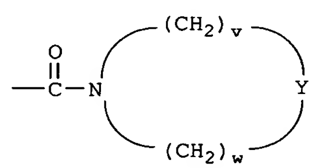
X_1 is 

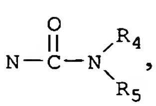
where Y is $N-\overset{O}{\overset{\|}{C}}-A_3-R_7$, $N-\overset{O}{\overset{\|}{C}}-A_3-O-R_7$ (where A_3 is a bond)

and R_7 is alkyl (preferably (di-isopropyl) methyl)), cycloalkyl, aryl or arylalkyl, or Y is



More preferred are compounds of formula I where X_1 is as defined above and where:

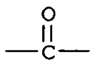
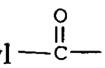
R_1 is carboxy, benzyloxycarbonyl,  where Y is

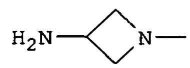
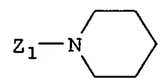
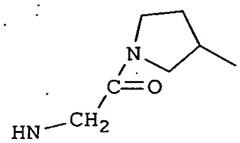


R_2 is hydrogen,

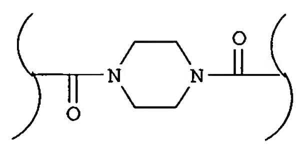
R_3 is hydrogen,

D is hydrogen,

A is , a bond, alkylene, -cycloheteroalkyl , or heteroaryl, such as pyridyl, and

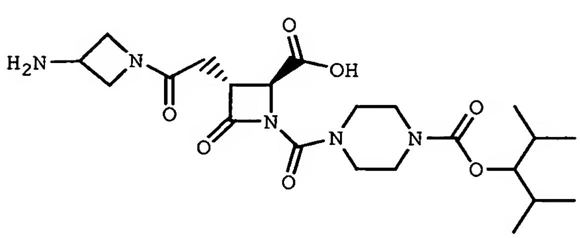
B is amino, cycloheteroalkyl, preferably ,  (where Z_1 is H, or NH_2CO- or alkyl), or , or heteroaryl, preferably pyridyl.

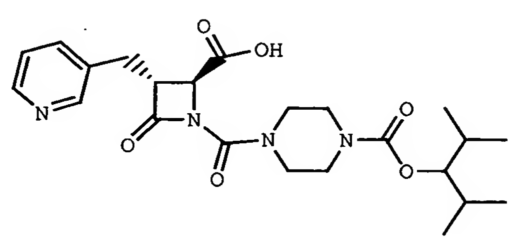
Most preferred are compounds of formula I where X_1 includes the moiety

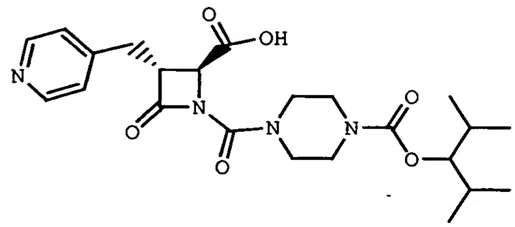
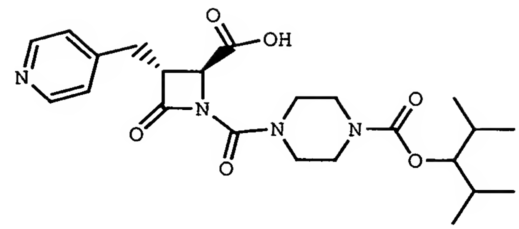


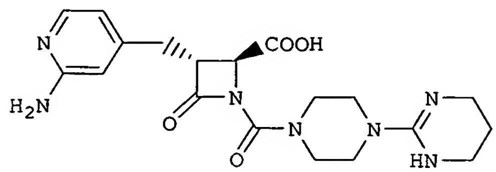
In the compounds of formula I of the invention and intermediates disclosed herein, the A_1, A_2, and A_3 groups as employed to define various substituents in the same compound or different compound may be the same or different and are independently selected from the various groups covered by the A_1, A_2, and A_3 groups.

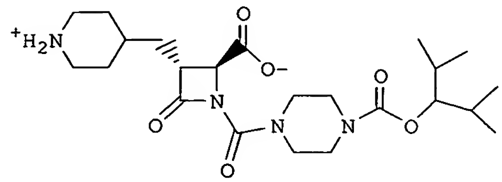
Examples of preferred compounds include the following:

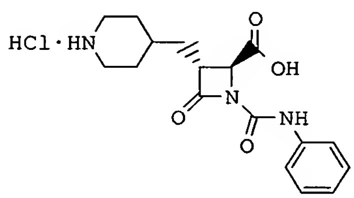
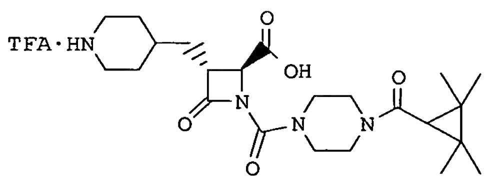
,

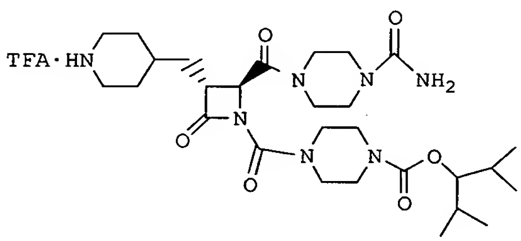
,

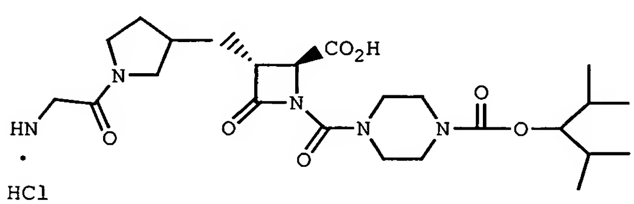

,

,

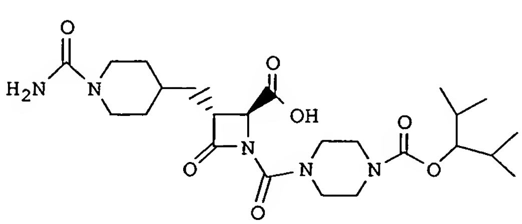
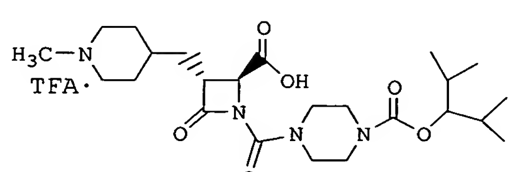


mono HCl, monoTFA salt
,

,

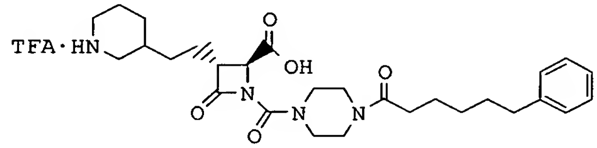

,

,


,

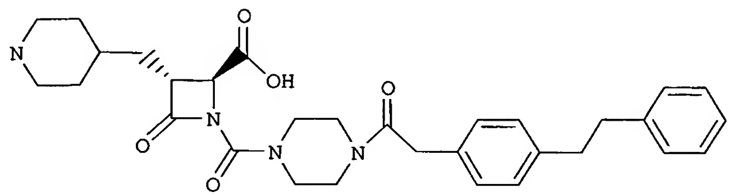

,


,

.

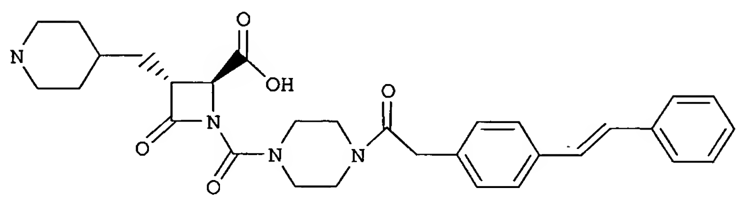
Examples of preferred compounds having tryptase inhibition activity include, but are not limited to,



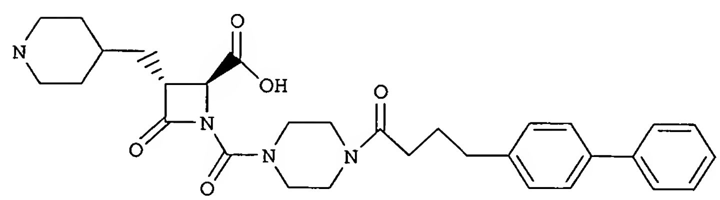
,



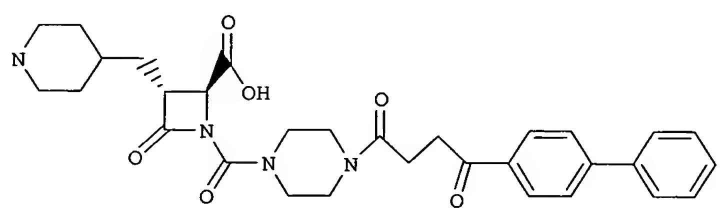
,



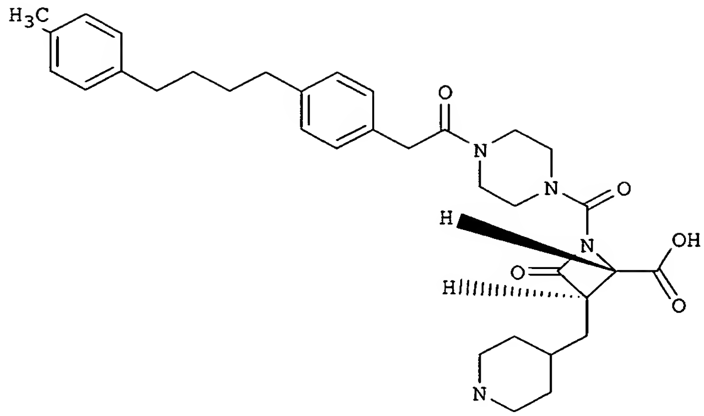
,



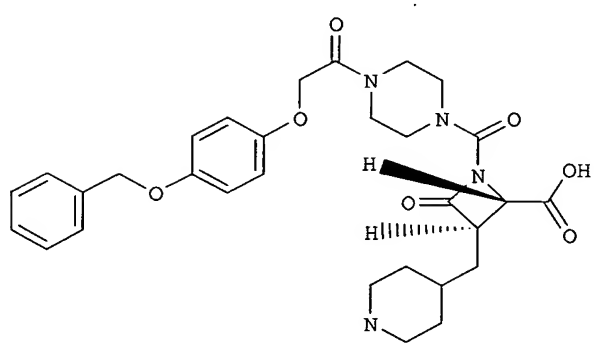
,



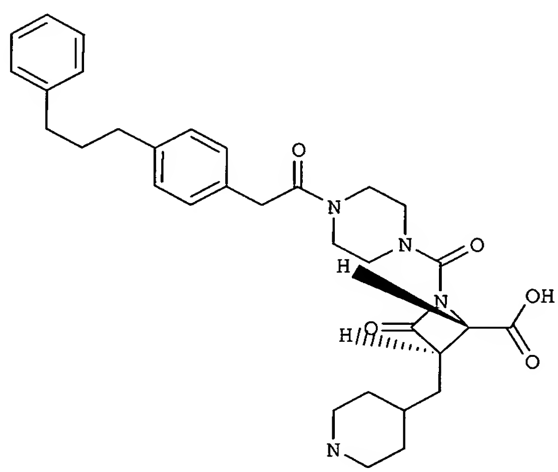
,



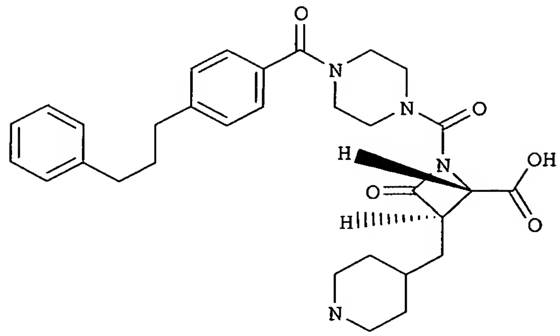
,



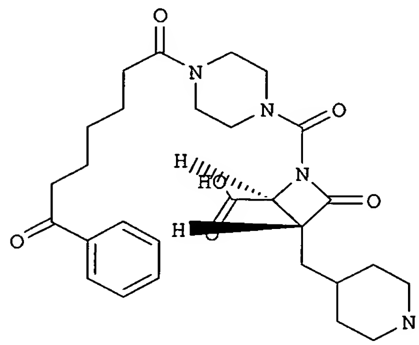
,



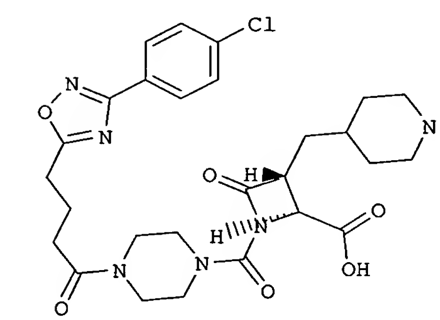
,



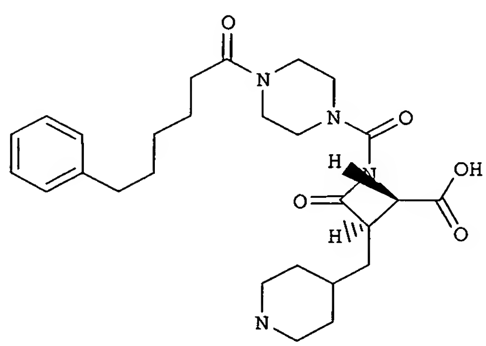
,



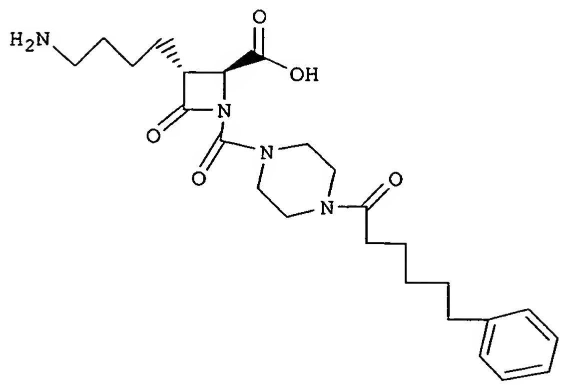
,



,



,



In addition, in accordance with the present invention, a method is provided for treating and/or preventing medical conditions in a mammalian species such as humans, dogs and cats, related to tryptase, thrombin, trypsin, Factor Xa, Factor VIIa, or urokinase-type plasminogen activator and/or treating and/or preventing asthma, including acute asthma and chronic asthma, or allergic rhinitis, wherein a therapeutically effective amount of a compound of formula I (which may or may not be limited by provisos I. and II. set out above) is administered to mammalian species in need of treatment.

DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" includes "substituted alkyl" and refers to straight or branched chain radicals having up to ten carbon atoms which may include one or more substitutents as described below. The term "lower alkyl" refers to straight or branched radicals having up to four carbon atoms and is a preferred subgrouping for the term alkyl.

The term "substituted alkyl" refers to such straight or branched chain radicals of 1 to 10 carbons wherein one or more, preferably one, two or three, hydrogens have been replaced by a hydroxy, amino, cyano, halo, aryl, trifluoromethyl, nitro, -NH(lower alkyl), -N(lower alkyl)$_2$, alkoxy, alkylthio, carboxy, alkoxycarbonyl, aminocarbonyl, alkoxycarbonylamino, cycloalkyl, carboxamido, formyl or acyl.

The term "alkoxy" refers to such alkyl groups as defined above attached to an oxygen. The term "alkylthio" refers to such alkyl groups as defined above attached to

a sulfur. The terms “lower alkoxy” and “lower alkylthio” refer to such lower alkyl groups as defined above attached to an oxygen or sulfur.

The term “cycloalkyl” includes “substituted cycloalkyl” and refers to fully or partially saturated rings of 3 to 7 carbons, which may include one or more substitutents as described below.

The term “substituted cycloalkyl” refers to such rings of 3 to 7 carbons having one or more substituents selected from lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy, trifluoromethyl, nitro, cyano, amino, aryl, cycloalkyl, carboxamido, formyl, acyl, -NH(lower alkyl), -N(lower alkyl)$_2$, or carboxy as well as such rings fused to a phenyl ring such as tetrahydronaphthyl.

The term “aryl” includes substituted aryl and refers to phenyl, 1-naphthyl and 2-naphthyl, which may include one or more substitutents as described below.

The term “substituted aryl” refers to phenyl, 1-naphthyl, and 2-naphthyl having a substituent selected from alkyl of 1 to 10 carbons, lower alkyl, lower alkoxy, lower alkylthio, halo, hydroxy, trifluoromethyl, nitro, amino, aminoalkyl, cycloalkyl, carboxamido, formyl, acyl, -NH(loweralkyl), -N(lower alkyl)$_2$, or carboxy, aryl, and di and tri-substituted phenyl, 1-naphthyl, or 2-naphthyl wherein said substituents are selected from methyl, methoxy, methylthio, halo, hydroxy and amino.

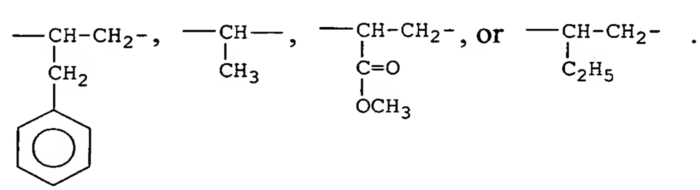
The term “heteroaryl” refers to unsaturated and partially saturated rings of 4 to 7 atoms containing one or two O and S atoms and/or one to four N atoms, one to three N atoms when the ring is 4 atoms, provided that the total number of hetero atoms in the ring is 4 or less, 3 or less when the ring is 4 atoms. The heteroaryl ring is attached by way of an available carbon or nitrogen atom. Preferred heteroaryl groups include 2-,3-, or 4-pyridyl, 4-imidazolyl,4-thiazolyl, 2- and 3-thienyl, 2- and 3-furyl, and 2-(1,4,5,6-tetrahydropyrimidinyl). The term heteroaryl also includes bicyclic rings wherein the 4 to 7 membered ring containing O, S and N atoms as defined above is fused to a benzene, cycloalkyl, heteroaryl or heterocycloalkyl ring. Preferred bicyclic rings are 2- and 3-indolyl and 4- and 5-quinolinyl. The mono or bicyclic heteroaryl ring can also be additionally substituted at one, two, three or more available carbon atoms by a lower alkyl, aryl, halo, carboxy, amino, hydroxy, A_2-lower alkoxy, A_2-guanido, benzyl, keto, cycloalkyl, carboxamido, formyl, acyl, or cyclohexylmethyl. Also, if the mono or bicyclic ring has an available N-atom such N atom can also be

substituted by an N-protecting group such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzyl or benzhydryl.

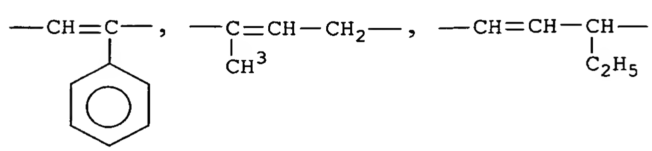
The term “heterocycloalkyl” or “cycloheteroalkyl” refers to fully saturated rings of 4 to 7 atoms containing one or two O and S atoms and/or one to four N atoms, one to three N atoms when the ring is 4 atoms, provided that the total number of hetero atoms in the ring is 4 or less, 3 or less when the ring is 4 atoms. The heterocycloalkyl is attached by way of an available carbon or nitrogen atom. Preferred heterocycloalkyl groups include pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, morpholinyl, tetrahydro-1,2-thiazinyl, piperazinyl, piperidinyl, homopiperizinyl and azetidinyl. The term heterocycloalkyl also includes bicyclic rings wherein the 4 to 7 membered saturated ring containing O, S and N atoms as defined above is fused to a cycloalkyl, benzene, heteroaryl, or heterocycloalkyl ring. The mono or bicyclic heterocycloalkyl ring can also be substituted at one or more available carbon atoms by a lower alkyl, halo, carboxy, hydroxy, keto, amino, aryl, cycloalkyl, carboxamido, formyl, acyl, aminocarbonyl, aminoalkylcarbonyl, A_2-lower alkoxy, A_2-guanido, benzyl or cyclohexylmethyl. Also, if the mono or bicyclic heterocycloalky ring has an available N atom such N atom can also be substituted by an N-protecting group such as benzyloxycarbonyl, *tert*-butoxycarbonyl, benzyl or benzhydryl.

The term “halo” refers to chloro, bromo, fluoro and iodo.

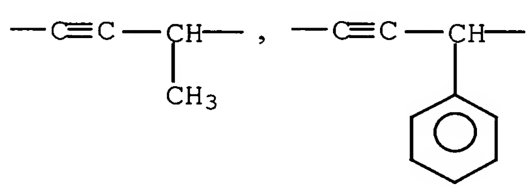
The terms “alkylene” and “substituted alkylene” refer to a bridge of 1 to 10 carbons such as $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_9-$, etc. One or more hydrogens, preferably one, in the alkylene bridge can be replaced by an alkyl, substituted alkyl, carboxy, alkoxycarbonyl, amino, -NH(lower alkyl), -N(lower alkyl)$_2$, hydroxy, aminocarbonyl, alkoxycarbonylamino, halo, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, hetereoaryl, or heterocycloalkyl, e.g.



The term "alkenyl" includes "substituted alkenyl" and refers to a bridge of 2 to 10 carbons having one or more double bonds, preferably 2 to 6 carbons with one double bond, such as -CH=CH-, -CH=CH-CH_2-, -CH_2-CH=CH-, etc. One or more hydrogens, preferably one, in the alkenyl bridge can be replaced by an alkyl, substituted alkyl, carboxy, alkoxycarbonyl, amino, -NH(lower alkyl), -N(lower alkyl)$_2$, hydroxy, aminocarbonyl, alkoxycarbonylamino, halo, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, or heterocycloalkyl, e.g.

 and the like.

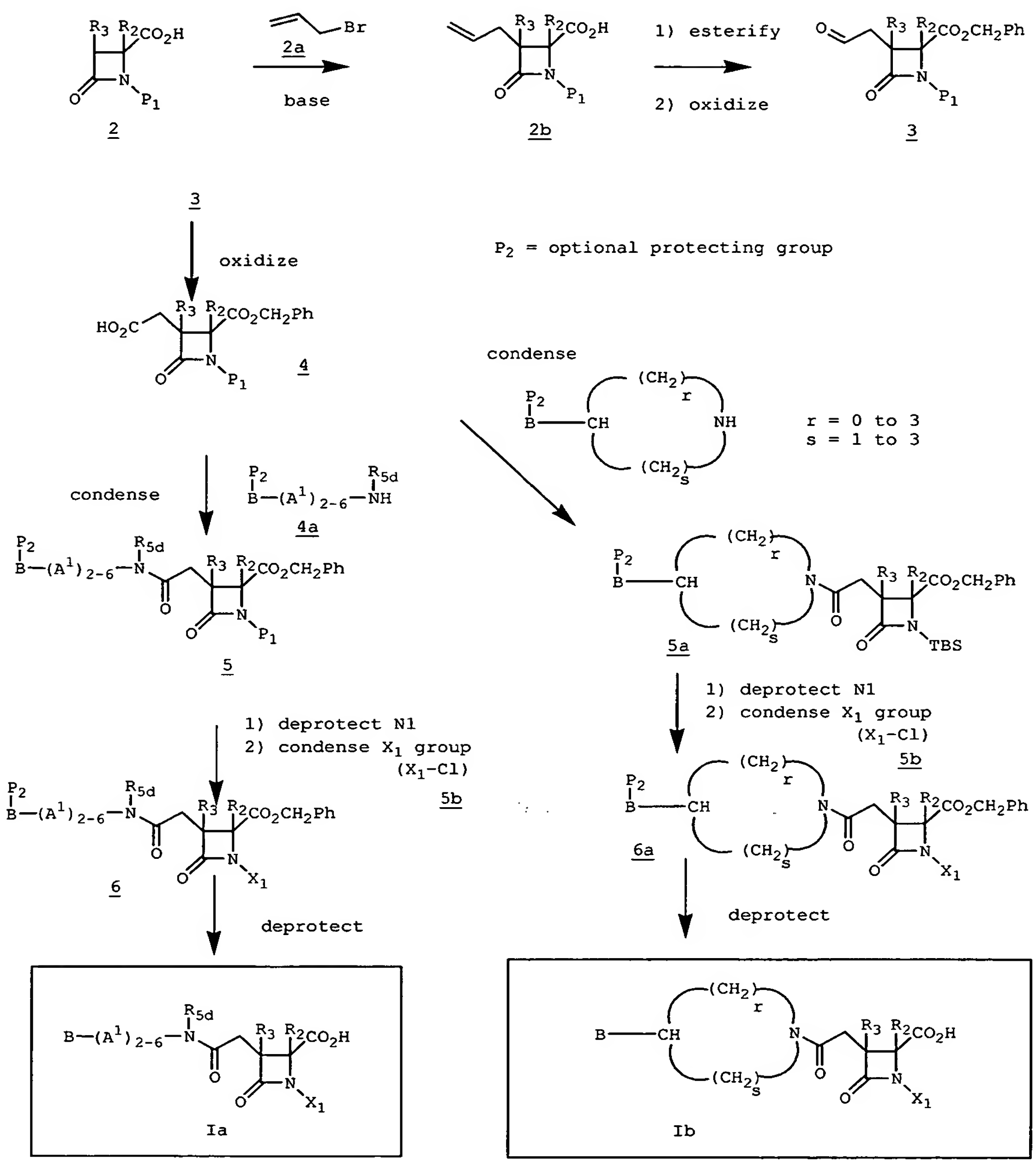
The term "alkynyl" and "substituted alkynyl" refer to a bridge of 2 to 10 carbons having one or more triple bonds, preferably 2 to 6 carbons with one triple bond, such as –C=C-, -CH_2-C=C-, -C=C-CH_2-, etc. One or more hydrogens in the alkynyl bridge can be replaced by an alkyl, substituted alkyl, carboxy, alkoxycarbonyl, amino, carboxy, alkoxycarbonyl, amino, -NH(lower alkyl), -N(lower alkyl)$_2$, hydroxy, aminocarbonyl, alkoxycarbonylamino, halo, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heteroaryl, or heterocycloalkyl, e.g.

 and the like.

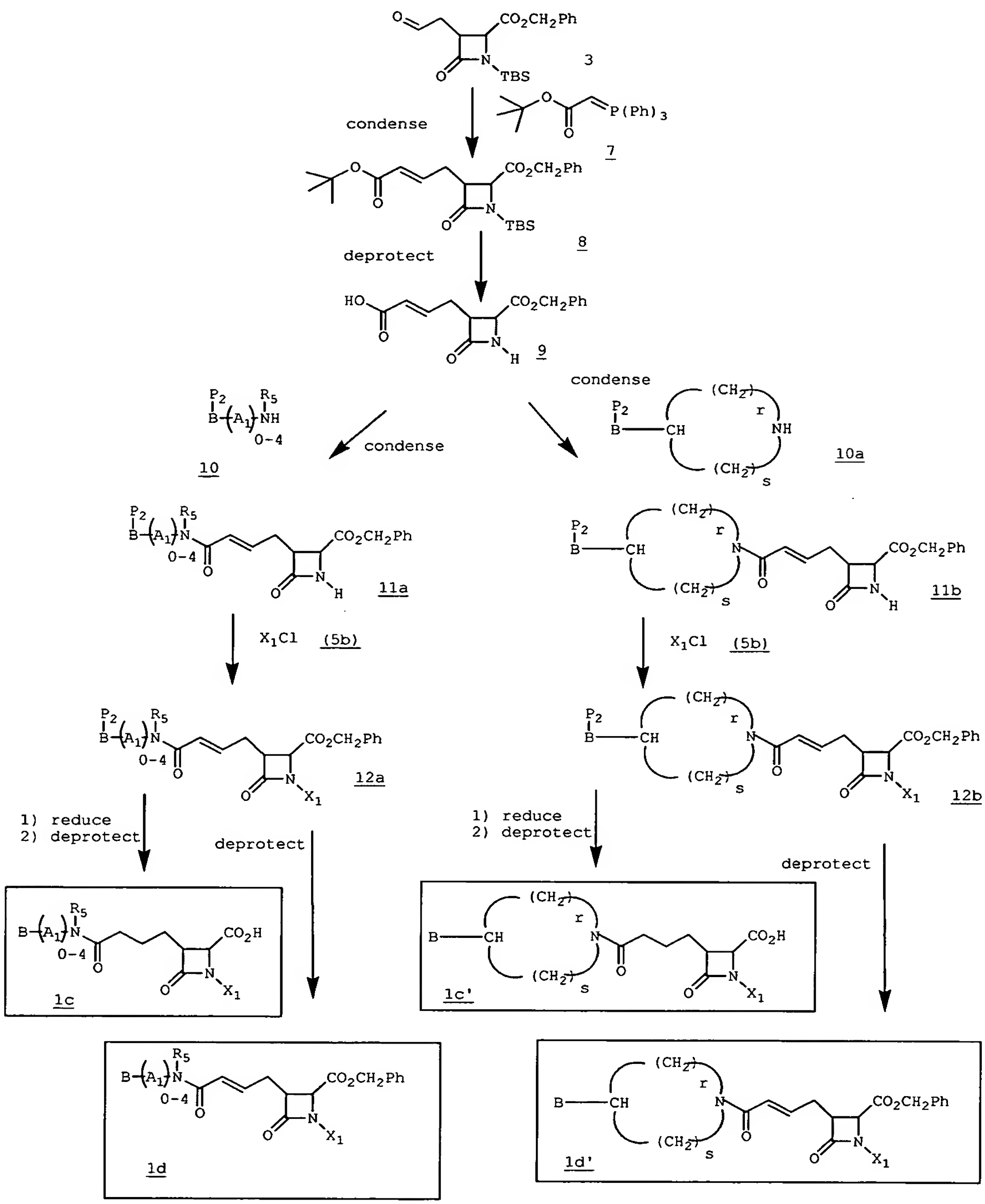
The term "acyl" refers to alkyl, aryl, alkenyl, heteroaryl, cycloheteroalkyl or cycloalkyl – attached to a carbonyl group.

Compounds of formula I may be prepared by the methods in the following Schemes.

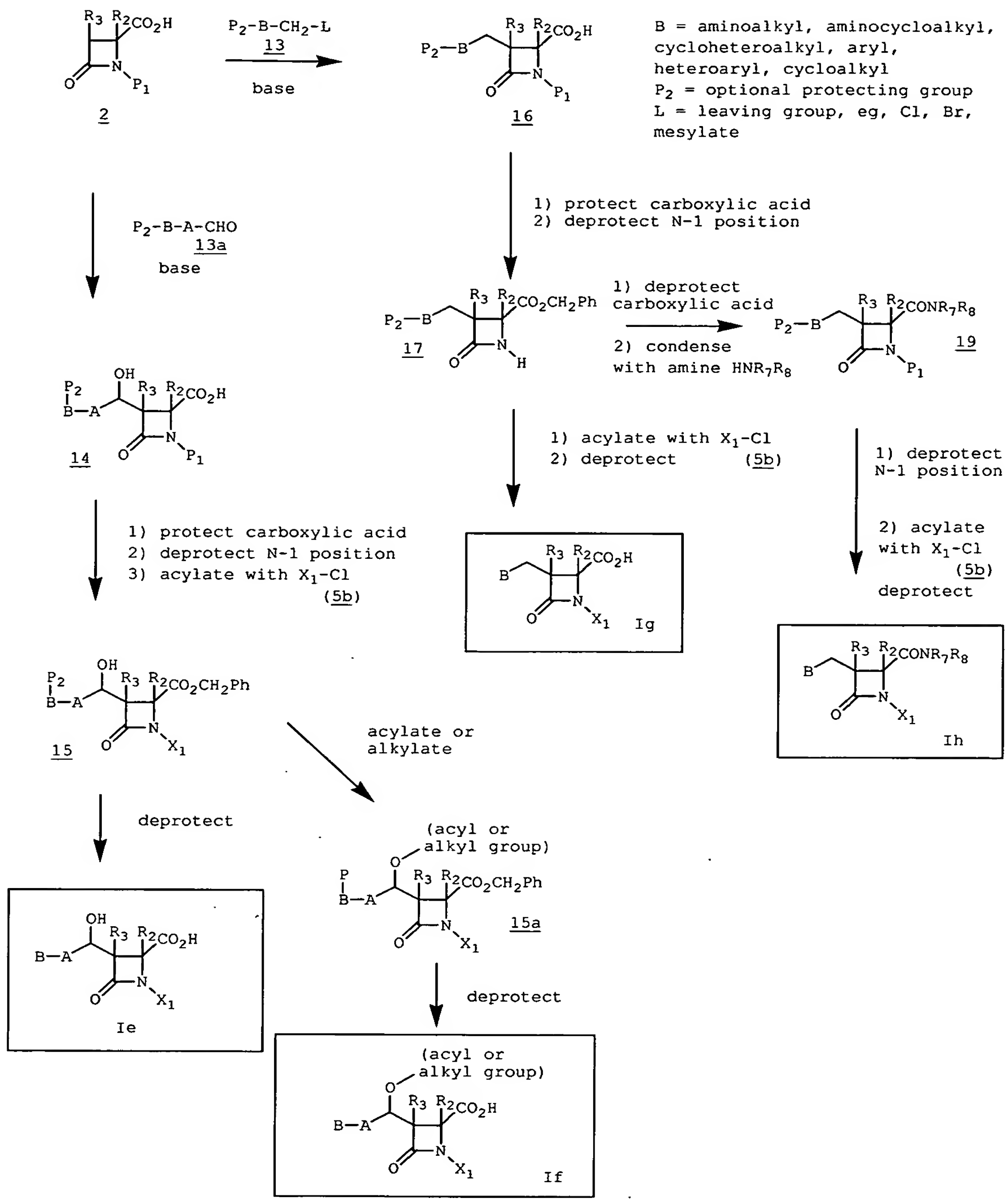
SCHEME 1



SCHEME 2


CO2CH2Ph
TBS
3
P(Ph)3
condense
7
8
deprotect
HO
9
condense
10
10a
11a
11b
X1Cl (5b)
12a
12b
1) reduce
2) deprotect
deprotect
1c
1c'
1d
1d'

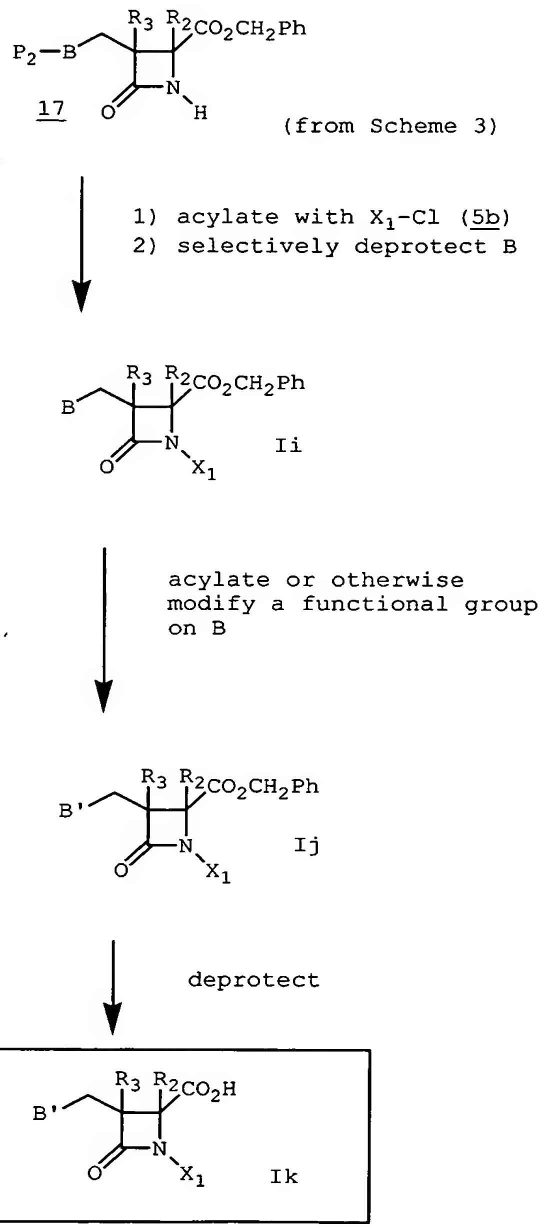
SCHEME 3



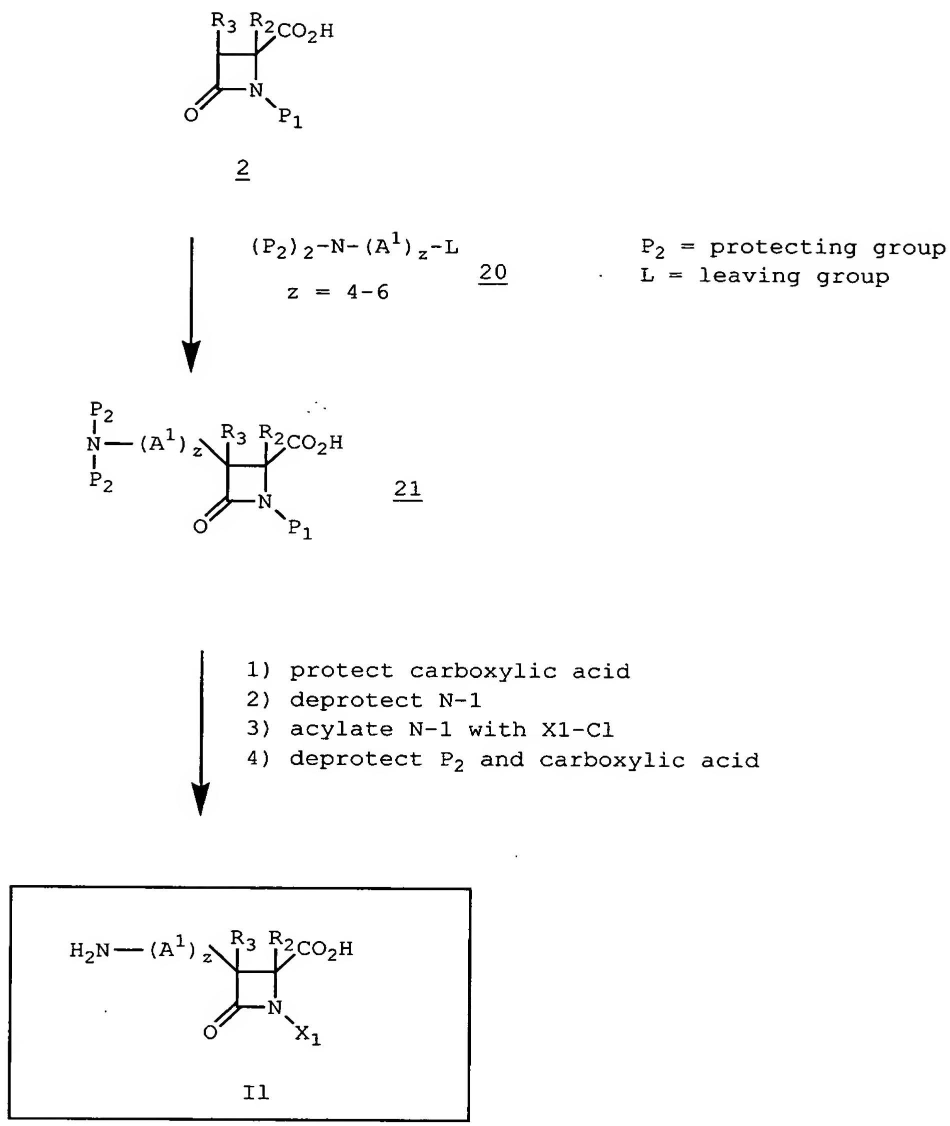
P_2-B-CH_2-L
13
base
B = aminoalkyl, aminocycloalkyl, cycloheteroalkyl, aryl, heteroaryl, cycloalkyl
P_2 = optional protecting group
L = leaving group, eg, Cl, Br, mesylate
2
16
P_2-B-A-CHO
13a
base
1) protect carboxylic acid
2) deprotect N-1 position
17
1) deprotect carboxylic acid
2) condense with amine HNR_7R_8
19
14
1) acylate with X_1-Cl
2) deprotect (5b)
1) deprotect N-1 position
2) acylate with X_1-Cl (5b)
deprotect
1) protect carboxylic acid
2) deprotect N-1 position
3) acylate with X_1-Cl (5b)
Ig
Ih
15
acylate or alkylate
deprotect
(acyl or alkyl group)
15a
Ie
deprotect
(acyl or alkyl group)
If

SCHEME 4

P_2 = optional protecting group
B' = substituted cycloalkyl,
cycloheteroalkyl, aryl, heteroaryl



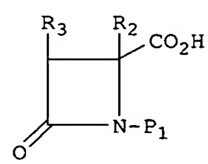
SCHEME 5


2
(P2)2-N-(A1)z-L
z = 4-6
20
P2 = protecting group
L = leaving group
21
1) protect carboxylic acid
2) deprotect N-1
3) acylate N-1 with X1-Cl
4) deprotect P2 and carboxylic acid
I1

Compounds of the invention of formula I wherein A includes an aminocarbonyl function (that is A^3) are prepared as shown in Scheme 1 and as described below.

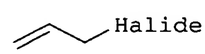
The carboxy substituted azetidinone of the formula 2

2



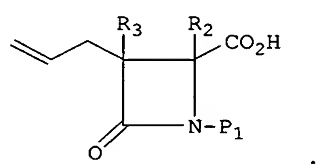
wherein P_1 is a silyl protecting group such as *tert*-butyldimethylsilyl (TBS) is treated with a propen-1-yl halide of the formula 2a

2a



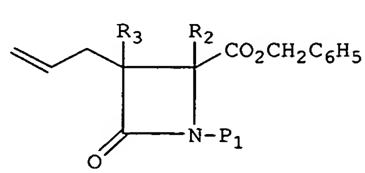
(preferably 3-bromo-1-propene) in the presence of base to give the carboxy substituted azetidinone of the formula 2b

2b

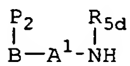
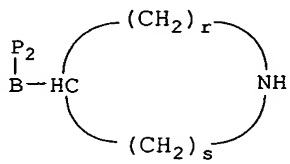


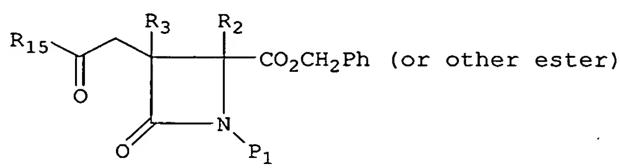
The carboxy substituted azetidinone of formula 2b is then treated esterified by treating 2b with benzyl alcohol and DCC or benzyl bromide and sodium bicarbonate to form ester 2c

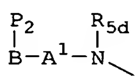
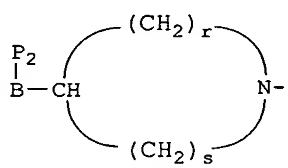
2c

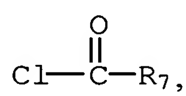
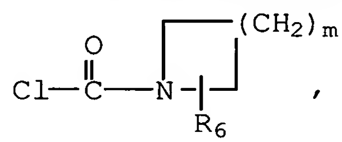


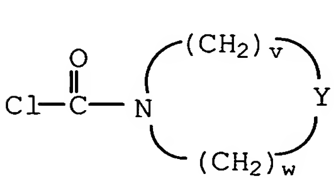
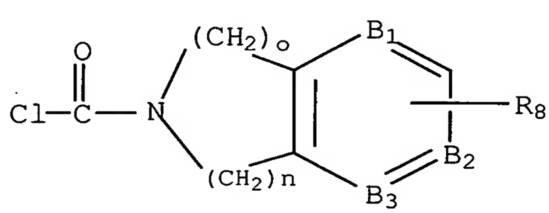
which is then oxidized by treating 2c with ozone and triphenylphospine to form azetidinone 3.

The azetidinone 3 is oxidized by treatment with potassium permanganate to form azetidinone 4. Coupling the azetidinone 4 with an amine selected from  (where P_2 is an optional protecting group such as BOC or Cbz or coupling 4 with 4a such as  gives the compound of the formula 5 or 5a

5 or 5a 

wherein R_{15} is  (5) or  (5a) .

Reacting the intermediate of formula 5 or 5a with ammonium fluoride removes the P_1 protecting group and condensing the deprotected intermediate with X_1-Cl (5b) compound selected from , ,

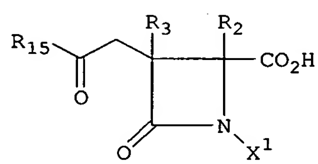
, ,

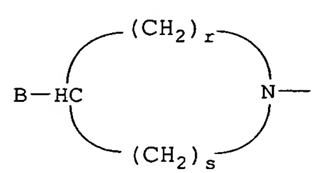
$Cl-\overset{O}{\overset{\|}{C}}-CH_2-O-R_{10}$, $Cl-\overset{O}{\overset{\|}{C}}-NH-SO_2-R_7$, $Cl-\overset{O}{\overset{\|}{C}}-\overset{R_9}{\overset{|}{N}}-A_2-\overset{R_9}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-R_4$,

$Cl-\overset{O}{\overset{\|}{C}}-alkyl-SO_2-R_7$, $Cl-\overset{O}{\overset{\|}{C}}-aryl-SO_2-R_7$,

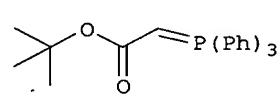
$Cl-\overset{O}{\overset{\|}{C}}-\overset{R_9}{\overset{|}{N}}-A_2-\overset{R_9}{\overset{|}{N}}-\overset{O}{\overset{\|}{C}}-OR_4$, or $Cl-SO_2-R_7$ or reacting with $OCN-SO_2-R_9$ gives the compound of the formula <u>6</u> or <u>6a</u>.

Removal of the B protecting group P_2 and the carboxylic acid protecting group gives the compounds of formula Ix

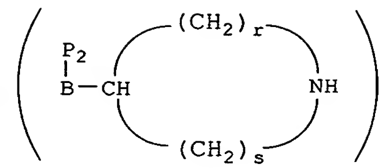
Ix 

where R_{15} is (Ia) $B-A^1-\overset{R_{5d}}{\overset{|}{N}}-$ or where R_{15} is (Ib)  .

Compounds of formula I of the invention wherein A is $-A^3-A^1-$ and B is amino, or A is $-A^2-A^1-$ and B is amino may be prepared as shown in Scheme 2 by condensing <u>3</u> with an ester of the structure <u>7</u>

<u>7</u> 

gives the azetidinone acid ester <u>8</u> which is deprotected by treating with ammonium fluoride followed by TFA to form azetidinone acid <u>9</u>.

Coupling 9 with amine 10 or with 10a  gives protected intermediates 11a and 11b, respectively.

Reacting the intermediate 11a and 11b with X_1-Cl compound of the formula 12a and 12b, respectively.

Compounds 12a and 12b are reduced by reaction with hydrogen and palladium as carbon and then deprotected by reaction with TFA to give compounds of the invention Ic and Ic′ respectively.

Where compounds 12a and 12 b are deprotected by reaction with TFA, compound of the invention Id and Id′ are produced respectively.

Compounds of formula I of the invention where D is OR^a may be prepared as shown in Scheme 3.

Azetidinone 2 is treated with aldehyde compound 13a in the presence of a base such as NaHMDS or LDA to form the intermediate 14. The carboxylic acid portion of 14 is protected by treating 14 with benzyl alcohol and DDC or benzyl bromide and $NaHCO_3$ to form an ester. The P_1 nitrogen protecting group is removed from the ester by treating the ester with ammonium fluoride. The resulting intermediate is treated with an X_1Cl compound 5b (as employed to react with intermediate 11 in Scheme 2) to form compound 15 which is deprotected by reaction with hydrogen with palladium or carbon and treatment with TFA or HCl in dioxane to form compound Ie of the invention.

Alternatively compound 15 may first be acylated or alkylated to form compound 15a which is deprotected by treating with hydrogen with palladium or carbon and treatment with TFA or HCl in dioxane to form compound If of the invention.

Compounds of formula I of the invention where A is a bond may be prepared as shown in Scheme 3 as follows: Azetidinone 2 is treated with reactant 13 in the presence of a base such as NaHMDS or LDA to form intermediate 16. Protection of

the carboxylic acid of 16 by reacting 16 with benzyl alcohol and DCC or benzyl bromide and $NaHCO_3$ and deprotection of the N-1 position by reacting acid protected 16 with ammonium fluoride or tetrabutyl ammonium fluoride produces intermediate 17. Intermediate 17 is acylated with an X_1Cl compound 5b (as employed to react with intermediate 11 in Scheme 2) and the P_2 protecting group and carboxylic acid protecting group are removed by reaction by either catalytic hydrogenation or sequential catalytic hydrogenation and treatment with TFA to form the compound of the invention Ig.

Compounds of the invention wherein A is a bond and R_1 is an aminocarbonyl may be prepared as shown in Scheme 3 as follows. The carboxylic acid protecting group in intermediate 17 is removed by catalytic hydrogenation and the deprotected compound is condensed with amine HNR_7R_8 and subsequently acylated by reaction with X_1-Cl (5b) to give the azetidinone 19. Removal of the P_2 protecting group by reacting with TFA or HCl in dioxane gives the compound of the invention Ih.

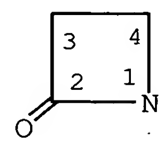
Compounds of the invention wherein A is a bond and B is as defined hereinbefore or B has a modified functional group (such as formed by acylation or reductive amination) is prepared as described in Scheme 4 as follows.

Azetidinone 17 is acylated with X_1-Cl (5b) as described hereinbefore and B is selectively deprotected by reacting with TFA or HCl in dioxane to form compound of the invention Ii. Compound Ii may then be acylated or a functional group or B may be modified (such as by acylation with an activated carboxylic acid or an isocyanate or by reductive amination with an aldehyde and palladium or carbon with hydrogen.) Acylation forms a compound of the invention Ij which is deprotected by reacting with catalytic hydrogenation to form compound of the invention Ik. Reductive amination in the presence of palladium on carbon and hydrogen results in concomitant deprotection of the carboxylic acid protecting group to give compound Ik.

Compounds of the invention of formula I wherein A is $(A)_z$ where z is 4 to 6 and B is amino may be prepared as shown in Scheme 5 as follows. Azetidinone 2 is treated with a protected amine alkylating agent 20 to form protected amine 21. The carboxylic acid of 21 is protected by reacting 21 with benzyl bromide and sodium bicarbonate and N-1 is deprotected by reacting with ammonium fluoride or tetrabutyl ammonium fluoride and N-1 is acylated by reacting with X_1-Cl (5b). The amine and

carboxylic acid protecting groups are removed together by catalytic hydrogenation or sequential treatment with TFA and catalytic hydrogenation to form amine compound of the invention Il.

The azetidinone compounds of formula I to Il and various intermediates and starting materials employed in their synthesis contain one or two asymmetric carbons as denoted below at ring positions 3 and 4



Of course, the compounds of formula I where R_1 and R_2 are the same and the compounds of formula I where R_1 is hydrogen contain only one asymmetric ring carbon. Additional asymmetric carbons may be present in the compounds of formula I to Il depending upon the definitions of the substituents R_1, A, X_1, R_2 and R_3. As is well known in the art, see for example J. March. Advanced Organic Chemistry, Fourth Edition, John Wiley & Sons, New York, NY (1991), pages 94-164, such asymmetric carbon atoms give rise to enantiomers and diastereomers, and all such stereoisomers, either in pure form or in the form of mixtures, are included within the scope of this invention. In addition, when alkenes are present in the compounds of formula I to Il, they may, when appropriately substituted exist as cis or trans isomers, or as mixtures thereof. Again, all such forms are within the scope of this invention.

The compounds of formula I to Il can be obtained as a pharmaceutically acceptable salt, as a physiologically hydrolyzable ester, or as a solvate. The compounds of formulas I to Il wherein R_1 is carboxy can exist in the form of an inner salt or zwitterion. All such forms are within the scope of this invention. Pharmaceutically acceptable salts include salts with mineral acids such as hydrochloric, hydrobromic, phosphoric and sulfuric as well as salts with organic carboxylic acids or sulfonic acids such as acetic, trifluoroacetic, citric, maleic, oxalic, succinic, benzoic, tartaric, fumaric, mandelic, ascorbic, malic, methanesulfonic, p-toluensulfonic and the like. Preparation of these acid addition salts is carried out by conventional techniques.

The novel compounds of formulas I to II of the invention possess tryptase inhibition activity. This activity was confirmed using either isolated human skin tryptase or recombinant human tryptase; prepared from the human recombinant beta-protryptase expressed by baculovirus in insect cells. The expressed beta-protryptase was purified using sequential immobilized heparin affinity resin followed by an immunoaffinity column using an anti-tryptase monoclonoal antibody. The protryptase was activated by auto-catalytic removal of the N-terminal in the presence of dextran sulfate followed by dipeptidyl peptidase I (DPPI) removal of the two N-terminal amino acids to give the mature active enzyme (Sakai et al., J. Clin. Invest., 97, pages 988 - 995, 1996). Essentially equivalent results were obtained using isolated native enzyme or the activated expressed enzyme. The tryptase enzyme was maintained in 2M sodium chloride, 10 nM 4-morpholinepropanesulfonic acid, pH 6.8.

The assay procedure employed a 96 well microplate. To each well of the microplate (Nunc MaxiSorp), 250 μl of assay buffer [containing low molecular weight heparin and tris (hydroxymethyl)aminomethane] was added followed by 2.0 μl of the test compound in dimethylsulfoxide. The substrate (10 μl) was then added to each well to give a final concentration of either 370 μM benzoyl-arginine-*p*-nitroaniline (BAPNA) or 100 μM benzyloxycarbonyl-glycine-proline-arginine-*p*-nitroaniline (CBz-Gly-Pro-Arg-pNA). Similar data was obtained using either substrate. The microplate was then shaken on a platform vortex mixer at a setting of 800 (Sarstedt TPM-2). After a total of three minutes incubation, 10 μl of the working stock solution of tryptase (6.1 mM final tryptase concentration for use with BAPNA or 0.74 nM for use with CBz-Gly-Pro-Arg-pNA) was added to each well. The microplate was vortexed again for one minute and then incubated without shaking at room temperature for an additional 2 minutes. After this time the microplate was read on a microplate reader (Molecular Devices UV max) in the kinetic mode (405 nm wavelength) over twenty minutes at room temperature. To determine the compound concentration that inhibited half of the enzyme activity (IC_{50}), the fraction of control activity (FCA) was plotted as a function of the inhibitor concentration (I) and curve to fit $FCA/(1 + [I]/IC_{50})$. The IC_{50} for each compound was determined 2 - 4 times and the obtained values were averaged.

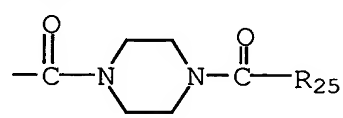
As a result of this tryptase activity, the compounds of formula I to Il as well as an inner salt thereof, a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof, are useful as antiinflammatory agents particularly in the treatment of chronic asthma and may also be useful in treating or preventing allergic rhinitis, inflammatory bowel disease, psoriasis, conjunctivitis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, and other chronic inflammatory joint diseases, or diseases of joint cartilage destruction. Additionally, these compounds may be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture. Additionally, these compounds may be useful for treating or preventing diabetic retinopathy, tumor growth and other consequences of angiogenosis. Additionally, these compounds may be useful for treating or preventing fibrotic conditions, for example, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas and hypertrophic scars.

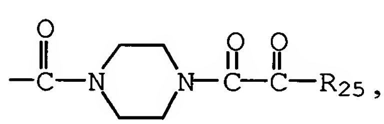
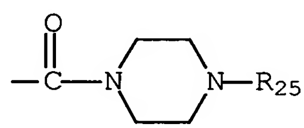
The compounds of formula I to Il are also inhibitors of Factor Xa and/or Factor VIIa. As a result, the compounds of formula I to VI as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may also be useful in the treatment or prevention of thrombotic events associated with coronary artery and cerebrovascular disease which include the formation and/or rupture of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, ischemia and angina (stable and unstable), deep vein thrombosis (DVT), disseminated intravascular coagulopathy, Kasacach-Merritt syndrome, pulmonary embolism, myocardial infarction, cerebral infarction, cerebral thrombosis, transient ischemic attacks, atrial fibrillation, cerebral embolism, thromboembolic complications of surgery (such as hip or knee replacement, introduction of artificial heart valves and endarterectomy) and peripheral arterial occulsion and may also be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture. The compounds of formula I to Il possessing Factor Xa and/or Factor VIIa inhibtion activity may also be useful as inhibitors of blood coagulation such as during the preparation, storage and fractionation of whole blood.

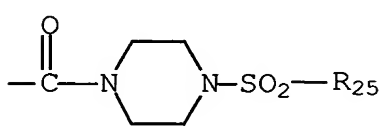
The compounds of formula I to Il are also inhibitors of urokinase-type plasminogen activator. As a result, the compounds of formula I to Il as well as an

inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may be useful in the treatment or prevention of restenosis and aneurysms, in the treatment or prevention of myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture, and may also be useful in the treatment of malignancies, prevention of metastases, prevention of prothrombotic complications of cancer, and as an adjunct to chemotherapy.

The compounds of formulas I to Il also possess thrombin and trypsin inhibitory activity similar to that reported by Han in the U.S. patents noted previously for the compounds of formula I to Il. As a result, the compounds of formula I to Il as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may be useful in treating or preventing pancreatitis, in the treatment or prevention of thrombotic events associated with coronary artery and cerebrovascular disease as described above, and may also be useful as inhibitors of blood coagulation such as during the preparation, storage, and fractionation of whole blood.

Certain compounds of formulas I to Il are also useful due to their selective tryptase inhibition activity. These compounds while having potent tryptase inhibition activity are much less active against other enzyme systems including trypsin, thrombin and Factor Xa. For example, this selective tryptase activity is seen with the compounds of formulas I to Il where X_1 is the group ,

,  or

 and R_{25} is a spacer terminating in a lipophilic group. Suitable spacers include groups of 3 or more atoms such as $—(CH_2)_{3\ to\ 10}—$,

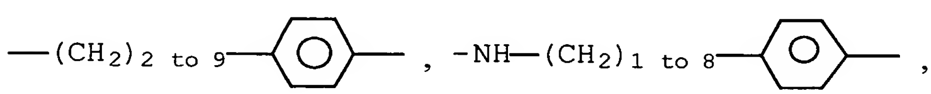
$-O-(CH_2)_{2\text{ to }9}-$, $-NH-(CH_2)_{2\text{ to }9}-$,

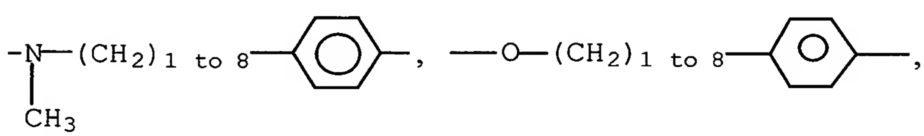
$-(CH_2)_{0\text{ to }7}-NH-C(=O)-NH-$, $-(CH_2)_{2\text{ to }9}-O-$,

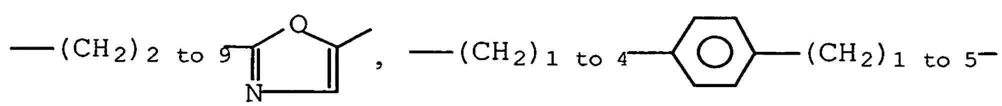
$-O-(CH_2)_{1\text{ to }8}-O-$, $-C(=O)-NH-(CH_2)_{1\text{ to }8}-$,

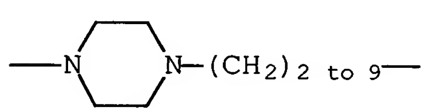
$-N(CH_3)-(CH_2)_{2\text{ to }9}-$, $-NH-(CH_2)_{1\text{ to }8}-O-$, and

$-N(CH_3)-(CH_2)_{1\text{ to }8}-O-$, etc., as well as groups containing 2 or more atoms and a phenyl, substituted phenyl, cycloalkyl, heteroaryl, or heterocycloalkyl ring such as






, and


, etc. Suitable lipophilic terminal groups include aryl, substituted aryl, cycloalkyl, heteroaryl, heterocycloalkyl, etc. These compounds of formulas I to II as well as an inner salt, a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof, are useful as anti-inflammatory agents

particularly in the treatment of chronic asthma and may also be useful in treating or preventing allergic rhinitis as well as some of the other diseases described above for the non-selective tryptase inhibitors. It is believed that as a result of their selective tryptase inhibition activity that these compounds will have less tendency to produce unwanted side-effects.

The compounds of formula I to Il as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof may be administered orally, topically, rectally or parenterally or may be administered by inhalation into the bronchioles or nasal passages. The method of administration will, or course, vary upon the type of disease being treated. The amount of active compound administered will also vary according to the method of administration and the disease being treated. An effective amount will be within the dosage range of about 0.1 to about 100 mg/kg, preferably about 0.2 to about 50 mg/kg and more preferably about 0.5 to about 25 mg/kg per day in a single or multiple doses administered at appropriate intervals throughout the day.

The composition used in these therapies can be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms such as tablets, pills, powders, liquid solutions or suspensions, liposomes, injectable and infusible solutions. Such compositions can include pharmaceutically acceptable carriers, preservatives, stabilizers, and other agents conventionally employed in the pharmaceutical industry.

When the compounds of formula I to Il as well as an inner salt or a pharmaceutically acceptable salt thereof, a hydrolyzable ester thereof, or a solvate thereof are employed to treat asthma or allergic rhinitis they will preferably be formulated as aerosols. The term "aerosol" includes any gas-borne suspended phase of the active compound which is capable of being inhaled into the bronchioles or nasal passage. Aerosol formulations include a gas-borne suspension of droplets of the active compound as produced in a metered dose inhaler or nebulizer or in a mist sprayer. Aerosol formulations also include a dry powder composition suspended in air or other carrier gas. The solutions of the active compounds of formulas I to Il used to make the aerosol formulation will be in a concentration of from about 0.1 to about 100 mg/ ml, more preferably 0.1 to about 30 mg/ml, and most preferably from about 1

to about 10 mg/ml. The solution will usually include a pharmaceutically acceptable buffer such as a phosphate or bicarbonate to give a pH of from about 5 to 9, preferably 6.5 to 7.8, and more preferably 7.0 to 7.6. Preservatives and other agents can be included according to conventional pharmaceutical practice.

Other pharmaceutically active agents can be employed in combination with the compounds of formula I to II depending upon the disease being treated. For example, in the treatment of asthma, β-adrenergic agonists such as albuterol, terbutaline, formoterol, fenoterol or prenaline can be included as can anticholinergics such as ipratropium bromide, anti-inflammatory cortiocosteroids such as beclomethasone, triamcinolone, flurisolide or dexamethasone, and anti-inflammatory agents such as cromolyn and nedocromil.

The following abbreviations are employed herein.

PVP = polyvinylpyrrolidone
Ph = phenyl
Bn = benzyl
BnOH = benzyl alcohol
t-Bu = tertiary butyl
Me = methyl
Et = ethyl
TMS = trimethylsilyl
TMS-NCO = trimethylsilylisocyanate
$TMSN_3$ = trimethylsilyl azide
TBS = tert-butyldimethylsilyl
FMOC = fluorenylmethoxycarbonyl
Boc = tert-butoxycarbonyl
Cbz = carbobenzyloxy or carbobenzoxy or benzyloxycarbonyl
THF = tetrahydrofuran
OSu = N-oxysuccinimide
Et_2O = diethyl ether (ether)
hex = hexanes
EtOAc = ethyl acetate

DMF = dimethyl formamide

MeOH = methanol

EtOH = ethanol

i-PrOH = isopropanol

DMSO = dimethyl sulfoxide

DME = 1,2 dimethoxyethane

DCE = 1,2 dichloroethane

HMPA = hexamethyl phosphoric triamide

HOAc or AcOH = acetic acid

TFA = trifluoroacetic acid

TFAA = trifluoroacetic anhydride

$i\text{-}Pr_2NEt$ = diisopropylethylamine

Et_3N = triethylamine

NMM = N-methyl morpholine

DMAP = 4-dimethylaminopyridine

$NaBH_4$ = sodium borohydride

$NaBH(OAc)_3$ = sodium triacetoxyborohydride

DIBALH = diisobutyl aluminum hydride

DIPEA = diisopropylethyl amine

TEA = triethylamine

DCM = 4-(dicyanomethylene)-2-methyl-6-(4-dimethylaminostyryl)-4H-pyran

NBS = N-bromosuccinimide

NaHMDS = sodium hexamethyldisilazide

DCC = 1,3-dicyclohexylcarbodiimide

LAH or $LiAlH_4$ = lithium aluminum hydride

n-BuLi = n-butyllithium

LDA = lithium diisopropylamide

Pd/C = palladium on carbon

PtO_2 = platinum oxide

KOH = potassium hydroxide

NaOH = sodium hydroxide

LiOH = lithium hydroxide

K_2CO_3 = potassium carbonate

$NaHCO_3$ = sodium bicarbonate

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)

HOAt = 1-Hydroxy-7-azabenzotriazole

Ph_3P = triphenylphosphine

$Pd(OAc)_2$ = Palladium acetate

Cbz-Cl = benzyl chloroformate

Ar = argon

N_2 = nitrogen

min = minute(s)

h or hr = hour(s)

L = liter

mL = milliliter

μL = microliter

g = gram(s)

mg = milligram(s)

mol = moles

mmol = millimole(s)

meq = milliequivalent

RT = room temperature

sat or sat'd = saturated

aq. = aqueous

TLC = thin layer chromatography

HPLC = high performance liquid chromatography

LC/MS = high performance liquid chromatography/mass spectrometry

MS or Mass Spec = mass spectrometry

NMR = nuclear magnetic resonance

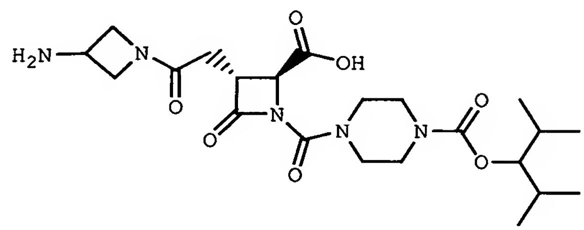
NMR spectral data: s = singlet; d = doublet; m = multiplet; br = broad; t = triplet

mp = melting point

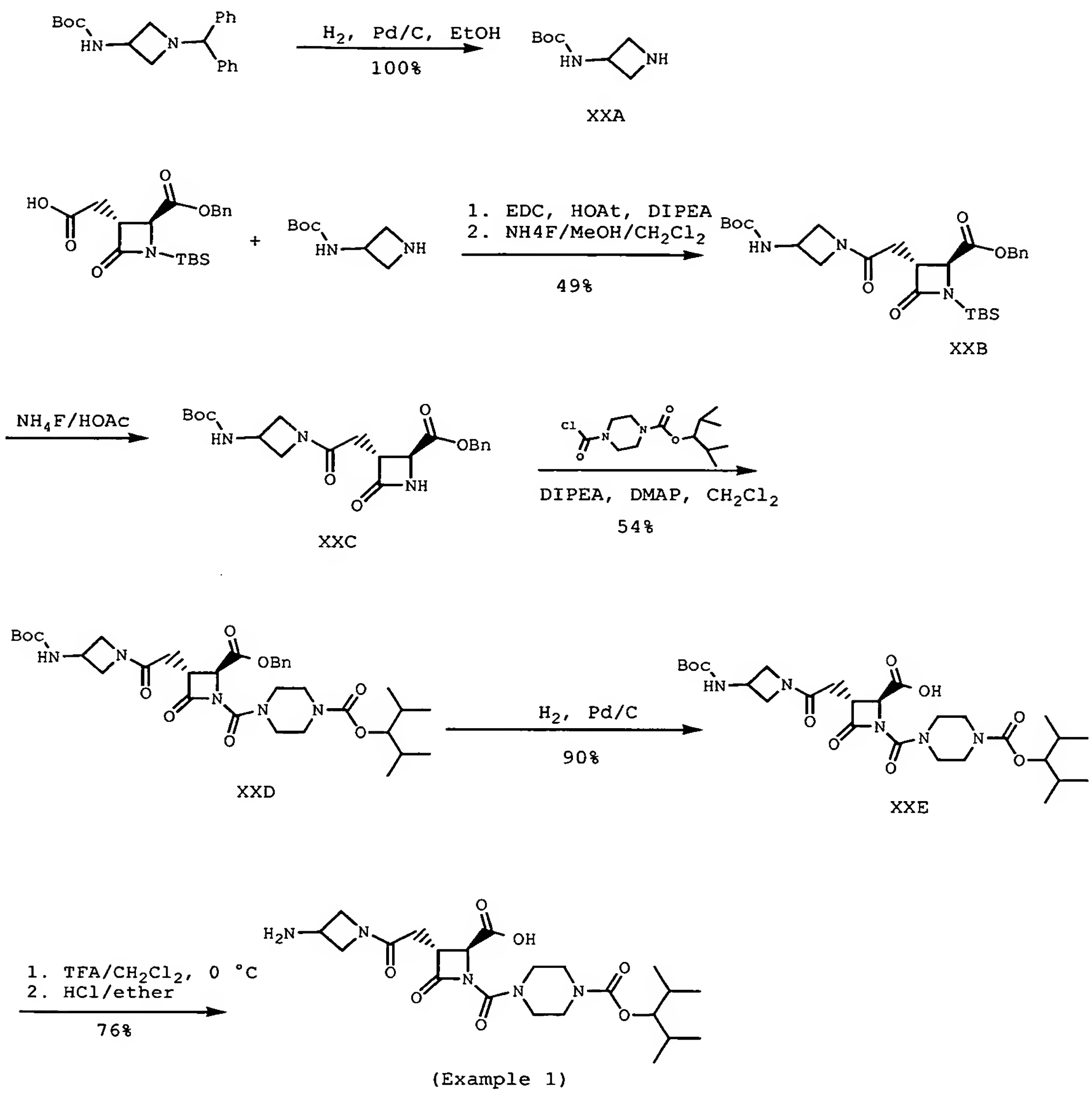
EXAMPLES

The following Examples represent preferred embodiments of the invention.

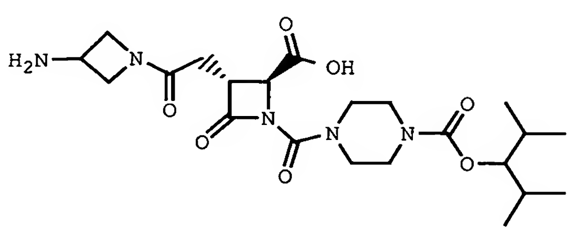
EXAMPLE 1



The title compound was prepared according to the following reaction sequence and as described below.



Boc
HN
N
Ph
Ph
H2, Pd/C, EtOH
100%
NH
XXA
HO
OBn
N
TBS
+
1. EDC, HOAt, DIPEA
2. NH4F/MeOH/CH2Cl2
49%
XXB
NH4F/HOAc
XXC
Cl
DIPEA, DMAP, CH2Cl2
54%
XXD
H2, Pd/C
90%
OH
XXE
1. TFA/CH2Cl2, 0 °C
2. HCl/ether
76%
H2N
(Example 1)

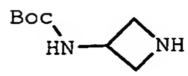


H2N
N
OH
N
N
N
O

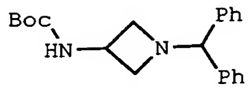
(Example 1)

Synthesis of Example 1 Compound

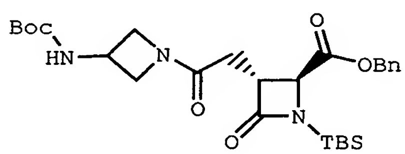
1. Step A



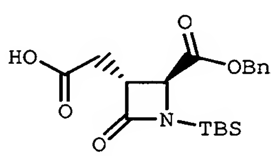
XXA

A mixture of  (113 mg, 0.33 mmol) and 10% Pd/C (88 mg) in ethanol (3 ml) was stirred under hydrogen atmosphere at rt for 2 h. The reaction mixture was filtered and evaporated to give XXA (63 mg) as a white solid.

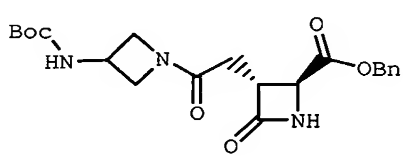
2. Step B



XXB

A mixture of  (101 mg, 0.27 mmol), XXA (57 mg), EDC (51 mg, 0.27 mmol) and (37 mg, 0.27 mmol) in DCM (2 ml) was stirred at rt for 3 h. The reaction was quenched with the addition of brine (10 ml). The mixture was then extracted with DCM (30 ml). The extract was dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography (silica, 0-4% MeOH/DCM) to give XXB (88 mg) as a colorless oil.

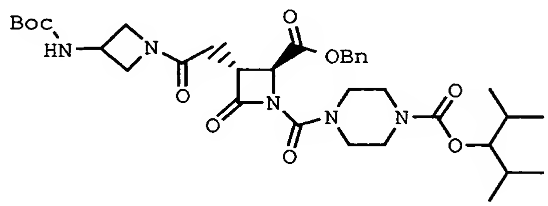
3. Step C



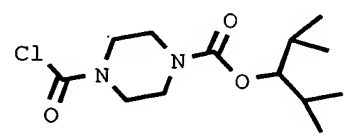
XXC

A solution of XXB(88 mg) was dissolved in DCM (1 ml) and the solution was treated with HOAc (20 μl) and NH_4F (0.5 M in MeOH, 340 μl) for 5 min. The mixture was concentrated and the residue was purified by flash chromatography (silica, 2-5% MeOH/DCM) to give XXC (55 mg) as a yellow foam.

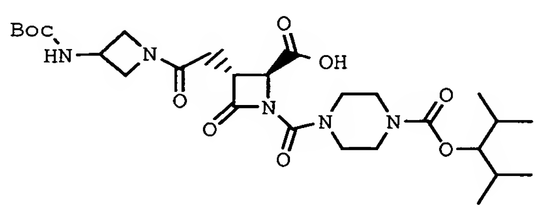
4. Step D



XXD

A mixture of XXC (52 mg, 0.12 mmol),  (42 mg, 0.14 mmol), DIPEA (24 μl, 0.14 mmol) and a few crystals of DMAP in DCM (1.5 ml) was stirred at rt for 4 h. The reaction was quenched with the addition of brine and extracted with DCM. The extract was dried ($MgSO_4$) and evaporated to give the crude product which was purified by flash chromatography (silica, 0-4% MeOH/DCM) to give XXD (44 mg) as a colorless solid.

5. Step E



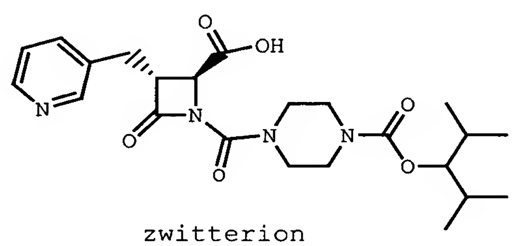
XXE

A mixture of XXD (41 mg, 0.061 mmol) and 10% Pd/C (15 mg) in ethanol (1 ml) was stirred under hydrogen atmosphere at rt for 1 h. The reaction mixture was filtered and evaporated to give XXE (32 mg).

6. **Step F (Example 1)**

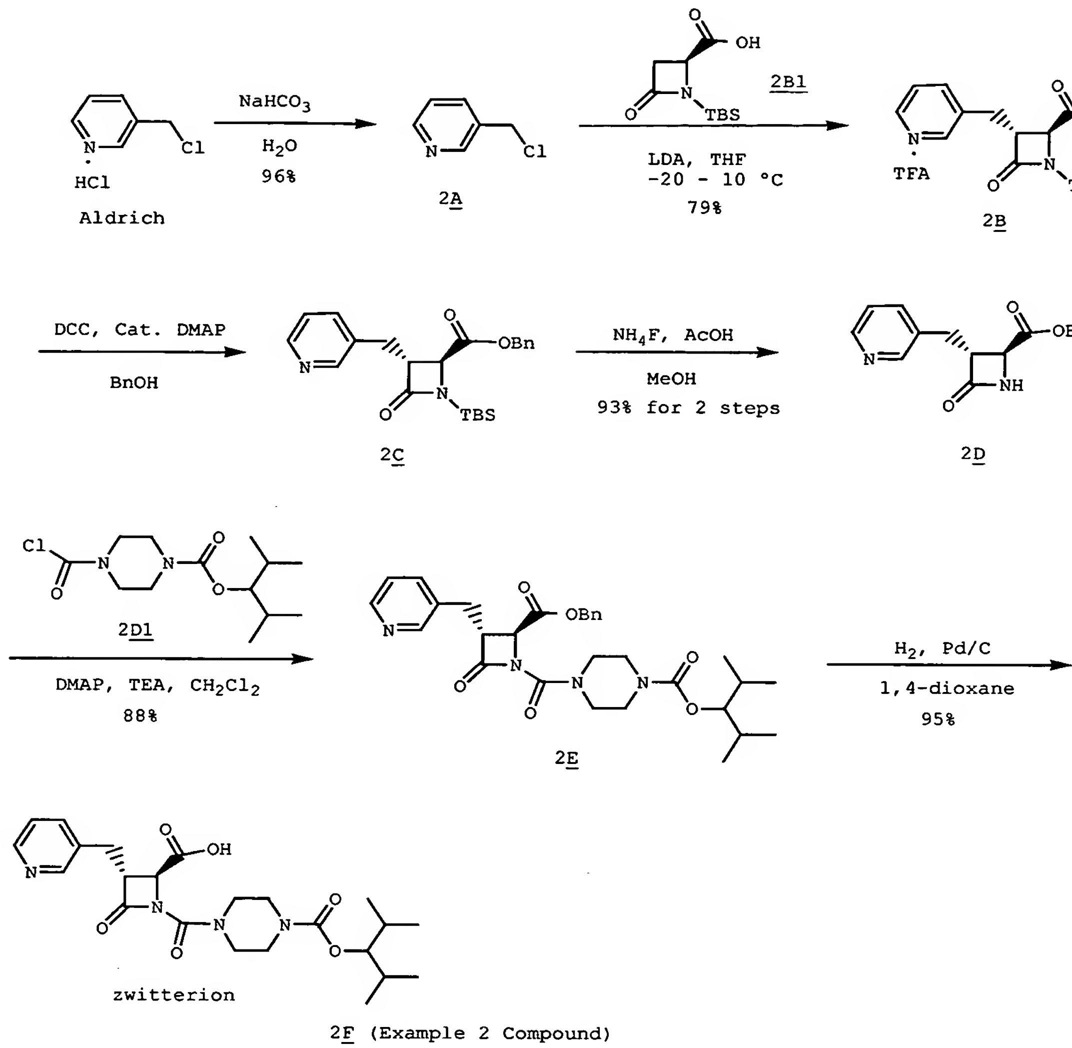
A solution of XXE (31 mg, 0.053 mmol) in DCM (0.75 ml) was cooled to –5 °C and treated with TFA (250 μl). The mixture was stirred at 0 °C for 5 min and then treated with HCl (53 μl, 1 N in Et_2O). The reaction was stirred at 0 °C until completion. The mixture was evaporated and the residue was dissolved in water to give Example 1 compound (27 mg) as a white solid.

EXAMPLE 2



zwitterion

The title compound was prepared according to the following reaction scheme and as described below.



Synthesis of Example 2 Compound

1. Preparation of 2A

To a solution of 3-picolyl chloride hydrochloride (1.00 g, 6.10 mmol) in 10 mL of distilled water was added $NaHCO_3$ (0.77 g, 9.14 mmol) with stirring. The mixture was extracted with Et_2O (20mL x 3). The extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated to give the free amine 2A (0.76 g) as a colorless oil.

2. Preparation of 2B

To a solution of diisopropylamine (0.68 mL, 4.82 mmol) in 5 mL of THF was added BuLi (1.6 M, 2.88 mL,, 4.62 mmol) at –15 °C. The solution was cooled to –78 °C and stirred for 20 minutes. A solution of 2β-lactam B1 (500 mg, 2.20 mmol) in 2 mL of THF was added dropwise. The solution was warmed to –20 °C to –10 °C and stirred at this temperature for 30 minutes. Then a solution of 3-picolyl chloride (2A) (420 mg, 3.30 mmol) in 3 mL of THF was added. The reaction mixture was stirred for 2 hours and then quenched with TFA (0.17 mL, 2.20 mmol). THF was removed and the residue was purified by preparative HPLC (reverse phase, methanol, water, TFA) to provide (after lyophilization) alkylation product 2B (568 mg) as a white solid. MS 321.4 $(M+H)^+$.

3. Preparation of 2C

To a mixture of acid 2B (290 mg 0.67 mmol) and benzyl alcohol (0.21 mL, 2.00 mmol) was added DCC (206 mg, 1.00 mmol) and DMAP (16 mg, 0.13 mmol) at 0 °C and stirred for 5 minutes. Then ice bath was removed. The mixture was stirred at rt for 3 hours. 15 mL of CH_2Cl_2 was added. The precipitate was filtered and washed with CH_2Cl_2 (10mL x 2). The CH_2Cl_2 solution was concentrated to crude 2C.

4. Preparation of 2D

The crude 2C was dissolved in 5 mL of methanol. Acetic acid (0.12 mL, 2.14 mmol) and a solution of NH_4F (0.5 M, 1.3 mL, 0.67 mmol) in methanol was added. The solution was stirred for 1 hour. The solvents were replaced with 30 mL of CH_2Cl_2, washed with sat. $NaHCO_3$ solution (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 4 : 1, Rf = 0.25) to afford 2D (200 mg) as a white solid. MS 297.3 $(M+H)^+$.

5. Preparation of 2E

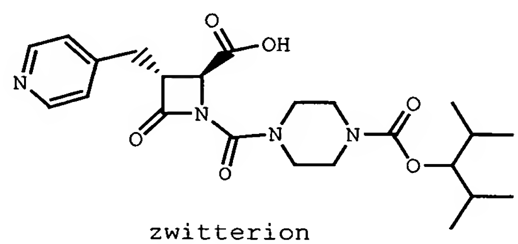
To a solution of ester 2D (150 mg, 0.51 mmol) in 4 mL of CH_2Cl_2 was added triethylamine (0.085 mL, 0.61 mmol), acid chloride 2D1 (176 mg, 0.61 mmol), and DMAP (4.0 mg, 0.031 mmol). The solution was stirred for 3 hour. The solvent was

removed. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 2 : 1, Rf = 0.22) to afford 2E (245 mg) as a white solid. MS 551.2 $(M+H)^+$.

6. Preparation of 2F (Example 2 Compound)

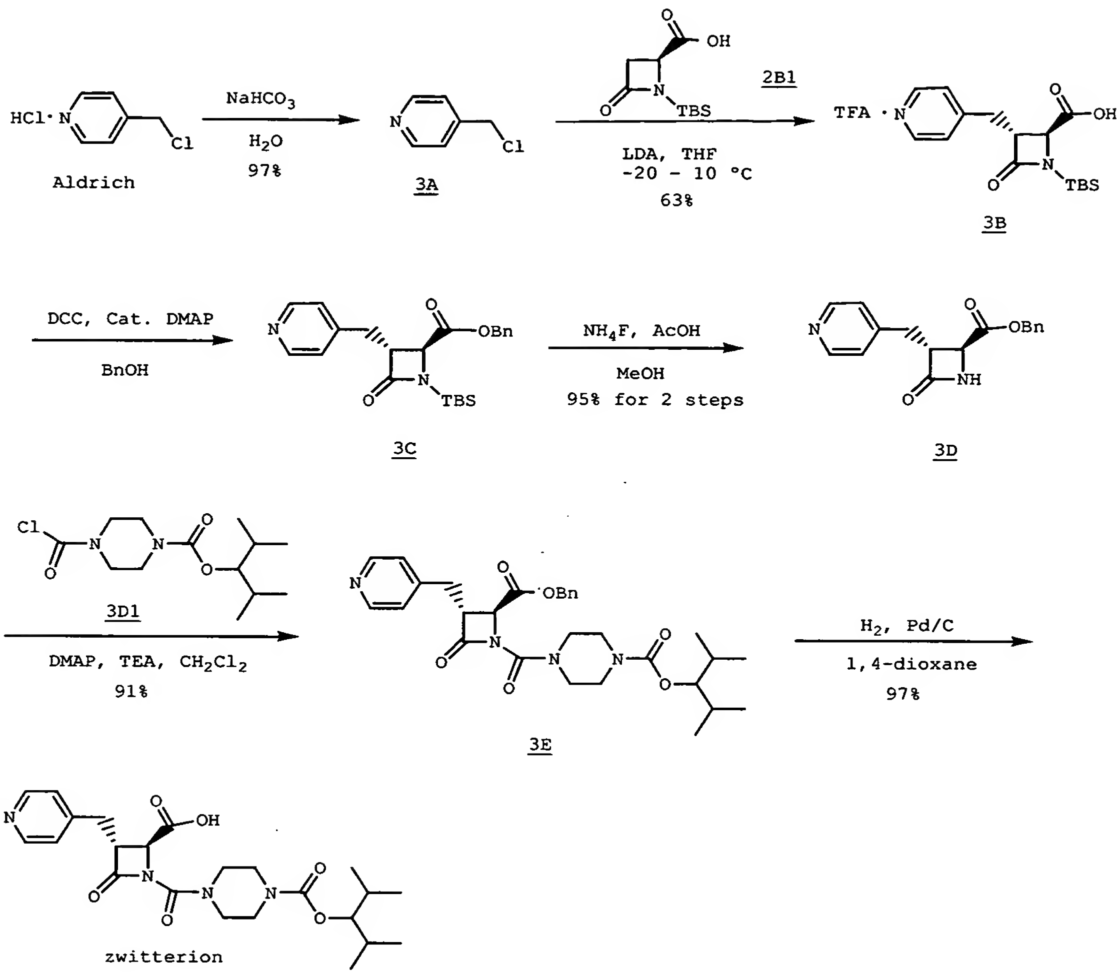
A mixture of 2E (100 mg, 0.18 mmol), Pd/C (10%, 60 mg) in dioxane (2 mL) was stirred under hydrogen atmosphere (hydrogen balloon) at room temperature for 3 hours. Analytical HPLC indicated the completion of the reaction. The reaction mixture was filtered through a celite pad, lyophilized to give Example 2 compound (79 mg, zwitterion) as a white foam. Purity by anal HPLC: 100%; MS: $(M+H)^+$ 461.2, $(M-H)^-$ 459.2; IR (KBr pellet) υ 1785 cm^{-1}.

EXAMPLE 3



zwitterion

The title compound was prepared according to the following reaction sequence and as described below.



3F (Example 3 Compound)

Synthesis of Example 3 Compound

1. Preparation of 3A

To a solution of 4-picolyl chloride hydrochloride (1.00 g, 6.10 mmol) in 10 mL of distilled water was added $NaHCO_3$ (0.77 g, 9.14 mmol) with stirring. The mixture was extracted with Et_2O (20mL x 3). The extracts were combined, washed with brine, dried over $MgSO_4$, and concentrated to give the free amine 3A (0.75 g) as a colorless oil.

2. Preparation of 3B

To a solution of diisopropylamine (0.68 mL, 4.82 mmol) in 5 mL of THF was added BuLi (1.6 M, 2.88 mL, 4.62 mmol) at –15 °C. The solution was cooled to –78 °C and stirred for 20 minutes. A solution of β-lactam 2B1 (500 mg, 2.20 mmol) in 2 mL of THF was added dropwise. The solution was warmed to –20 °C to –10 °C and stirred at this temperature for 30 minutes. Then a solution of 4-picolyl chloride (3A) (420 mg, 3.30mmol) in 3 mL of THF was added. The reaction mixture was stirred for 2 hours and then quenched with TFA (0.17 mL, 2.20 mmol). THF was removed and the residue was purified by preparative HPLC (reverse phase, methanol, water, TFA) to provide (after lyophilization) alkylation product 3B (453 mg) as white solid. MS 321.4 $(M+H)^+$.

3. Preparation of 3C

To a mixture of acid 3B (310 mg 0.71 mmol) and benzyl alcohol (0.23 mL, 2.14 mmol) was added DCC (309 mg, 1.50 mmol) and DMAP (17 mg, 0.14mmol) at 0 °C and stirred for 5 minutes. Then ice bath was removed. The mixture was stirred at rt for 3 hours. 15 mL of CH_2Cl_2 was added. The precipitate was filtered and washed with CH_2Cl_2 (10mL x 2). The CH_2Cl_2 solution was concentrated to crude 3C.

4. Preparation of 3D

The crude 3C was dissolved in 5 mL of methanol. Acetic acid (0.13 mL, 2.14 mmol) and a solution of NH_4F (0.5 M, 1.4 mL, 0.71 mmol) in methanol was added. The solution was stirred for 1hour. The solvents were replaced with 30 mL of CH_2Cl_2, washed with sat. $NaHCO_3$ solution (5 mL) and brine (5 mL), dried over $MgSO_4$, and concentrated. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 4 : 1, Rf = 0.25) to afford 3D (200 mg) as a white solid. MS 297.3 $(M+H)^+$.

5. Preparation of 3E

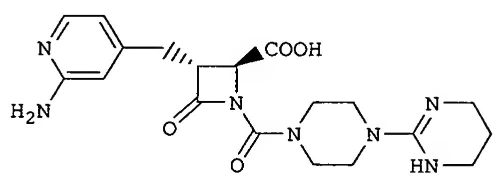
To a solution of ester 3D (120 mg, 0.41 mmol) in 4 mL of CH_2Cl_2 was added triethyl amine (0.068 mL, 0.49 mmol), acid chloride 3D1 (143 mg, 0.49 mmol), and DMAP (2.5 mg, 0.021 mmol). The solution was stirred for 3 hour 3 hour. The

solvent was removed. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 2 : 1, Rf = 0.22) to afford 3E (205 mg) as a white solid. MS 551.2 $(M+H)^+$.

6. **Preparation of 3F (Example 3 Compound)**

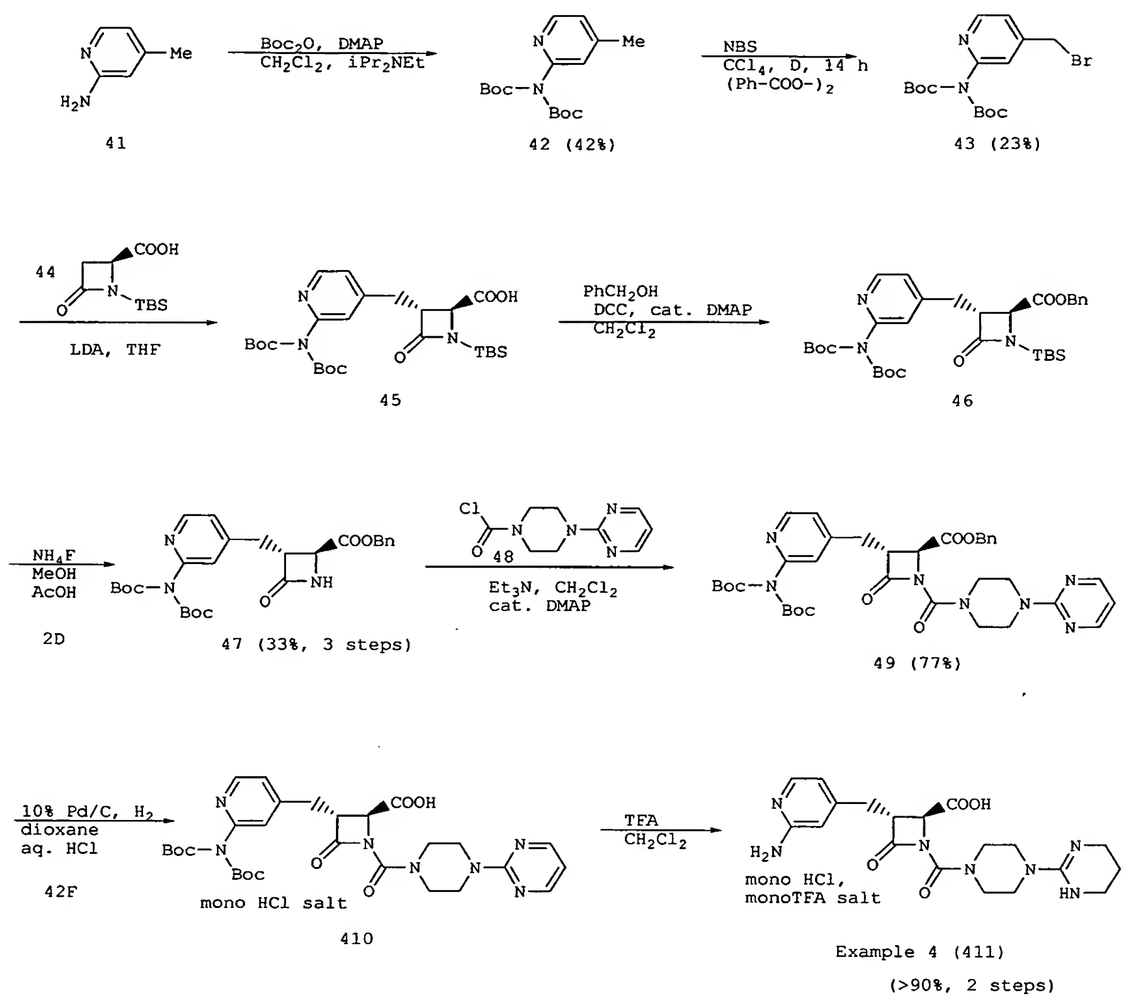
A mixture of 3E (100 mg, 0.18 mmol), Pd/C (10%, 60 mg) in dioxane (2 mL) was stirred under hydrogen atmosphere (hydrogen balloon) at room temperature for 3 hours. Analytical HPLC indicated the completion of the reaction. The reaction mixture was filtered through a celite pad, lyophilized to give Example 3 compound (80 mg, zwitterion) as a white foam. Purity by anal HPLC: 96%; MS: $(M+H)^+$ 461.2, $(M-H)^-$ 459.2; IR (KBr pellet) υ 1785 cm^{-1}.

EXAMPLE 4



mono HCl, monoTFA salt

The title compound was prepared according to the following reaction scheme and as described below.



Synthesis of Example 4 Compound

1. Preparation of 42

To a solution of 2-amino-4-picoline (41) (5.41 g, 50 mmol) in dichloromethane (100 mL) at 0 °C was added N,N-diisopropylethylamine (17.4 mL, 100 mmol), di-t-butyldicarbonate (27.3 g, 125 mmol), and DMAP (6.1 g, 50 mmol). After the addition, the reaction was stirred at room temperature for 16 hours and diluted with ethyl acetate. The organics were washed with saturated aqueous ammonium chloride (3x), brine (1x), saturated sodium bicarbonate (2x) and brine, dried (magnesium sulfate) and concentrated to a viscous oil (14.3 g). Purification of a 7.5 g portion of this oil over silica gel using dichloromethane-ethyl acetate (19:1) afforded 3.32 g of compound 42 as a solid.

2. Preparation of 43

A mixture of compound 42 (1.85 g, 6 mmol), carbon tetrachloride (30 mL), N-bromosuccinimide (NBS) (1.07 g, 6 mmol), and benzoyl peroxide (145 mg, 0.6 mmol) was refluxed for 14 hours, cooled, and filtered. Evaporation of the filtrate and concentration of the residue from dichloromethane (4x) gave an oil (2.37 g), which was flash chromatographed over silica gel using dichloromethane-ethyl acetate (19:1) to provide 534 mg of compound 43 as an oily residue.

3. Preparation of 45

To 0.32 mL (2.28 mmol) of diisopropylamine in 2 mL of tetrahydrofuran at -20 °C under argon was added 0.8 mL of 2.5 M n-butyl lithium in hexane (2 mmol). The mixture was stirred for 10 minutes and cooled to -70 °C. A solution of 229 mg (1.0 mmol) of compound 44 in 2 mL of tetrahydrofuran was added over 3 minutes and the reaction was warmed to -20 °C over 15 minutes. A solution of 526 mg (1.36 mmol) of compound 3 in 3 mL of tetrahydrofuran was added and the reaction was stirred between -20 °C and -30 °C for 5 hours and then stored at -40 °C for 16 hours. The reaction was warmed to 0 °C and quenched by addition of 10% potassium hydrogensulfate (5.5 mL) and then water and ethyl acetate. After a total of 3 extractions with ethyl acetate, the ethyl acetate was washed with brine, dried (sodium sulfate), and concentrated to give 730 mg of crude compound 45 as an oily residue.

4. Preparation of 46

A mixture of 540 mg of crude compound 45 above, dichloromethane (1.4 mL), benzyl alcohol (168 μL, 1.62 mmol), N,N'-dicyclohexylcarbodiimide (223 mg, 1.08 mmol), and DMAP (18 mg, 0.15 mmol) was stirred at room temperature for 5 hours and stored overnight at 5 °C. The solids were filtered off and the filtrate was concentrated to a residue, which was taken up in ethyl acetate. After 20 minutes, solids were removed by filtration and the filtrate was concentrated to give 732 mg of crude compound 46 as an oil.

5. Preparation of 47

A solution of 2.2 mL of 0.5 M ammonium fluoride in methanol (1.1 mmol) was added to a mixture of 732 mg of crude compound 46 above, methanol (5 mL), and acetic acid (190 µL, 3.3 mmol) and the mixture was stirred at room temperature for 1.5 hours and then concentrated to a residue. The residue was taken up in ethyl acetate and water and the pH was adjusted to 8.7 with aqueous 5% sodium bicarbonate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine (2x), dried (sodium sulfate) and concentrated to an oily solid. Ethyl acetate was added and after filtration the filtrate was concentrated to an oily residue (558 mg). Chromatography of the residue over silica gel using dichloromethane-ethyl acetate (75:25) afforded 125 mg of compound 47 as a residue.

6. Preparation of 49

A mixture of compound 47 (58 mg, 0.11 mmol), dichloromethane (1.5 mL), compound 48 (30 mg, 0.13 mmol), triethylamine (35 µL, 0.25 mmol), and DMAP (3 mg, 0.025 mmol) was stirred at room temperature for 16 hours. The reaction was concentrated and the residue was taken up in ethyl acetate, water, and several drops of 10% potassium hydrogensulfate. The pH was adjusted to 8.0 (aqueous sodium bicarbonate) and the ethyl acetate layer was separated and washed with water (2x), dried (sodium sulfate), and concentrated to an oil (84 mg). Chromatography of the oil over silica gel using dichloromethane-ethyl acetate (60:40) gave 59 mg of compound 49 as a residue.

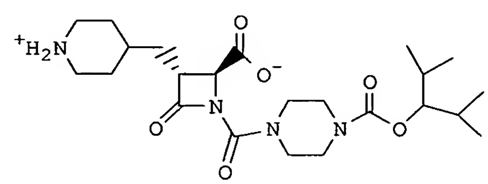
7. Preparation of 410

Compound 49 (57 mg, 0.081 mmol) was hydrogenated at 1 atmosphere in dioxane (4 mL) and 82 µL of aq. 1.0 N HCl (0.082 mmol), in the presence of 19 mg of 10% palladium on carbon for 2 hours. The reaction was filtered with aqueous dioxane and the filtrate was concentrated and lyophilized to give 49 mg of compound 410 as a white powder.

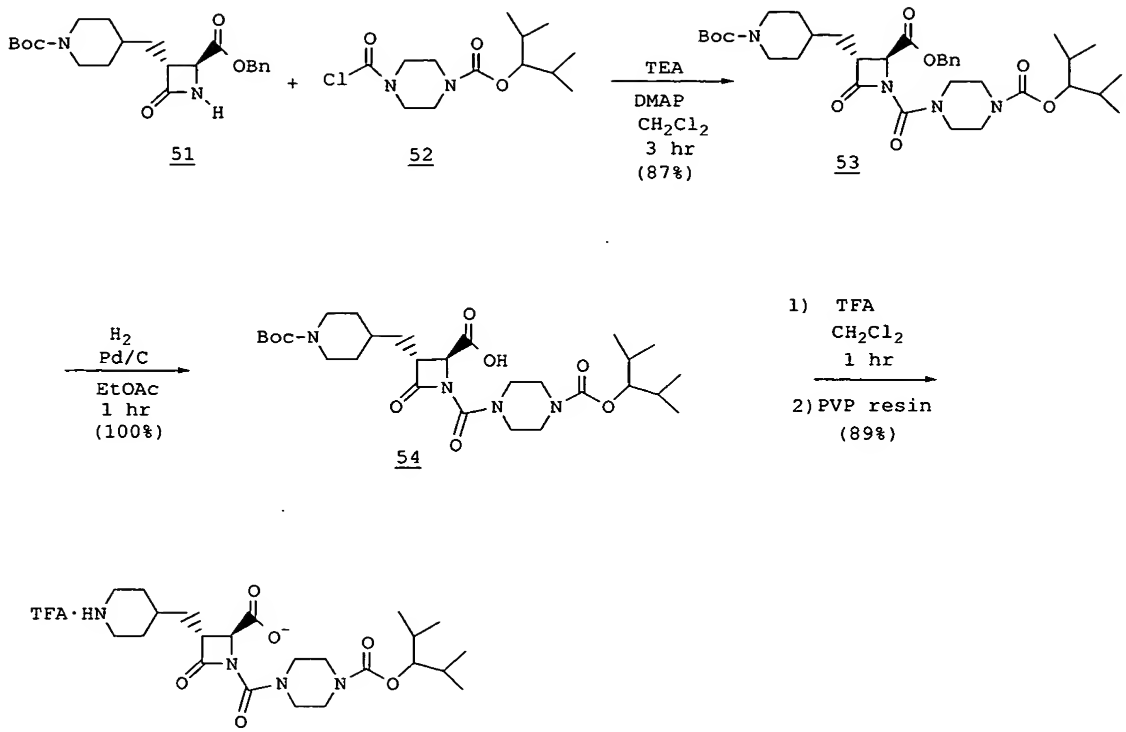
8. Preparation of 411 (Example 4 Compound)

Trifluoroacetic acid (0.15 mL) was added to a stirred solution of compound 410 (45 mg) in dichloromethane (2 mL) at 0-5 °C. The reaction was stirred at ambient temperature for 1.5 hours and 0.5 mL additional trifluoroacetic acid was added. After 1.5 hours, dioxane (5 mL) was added and the solution was concentrated and lyophilized from aqueous dioxane to give 44 mg of compound 411 (Example 4 compound) as a white solid; IR (KBr) 1789 cm^{-1} ; mass spectrum $(M+H)^+$ 416.

EXAMPLE 5



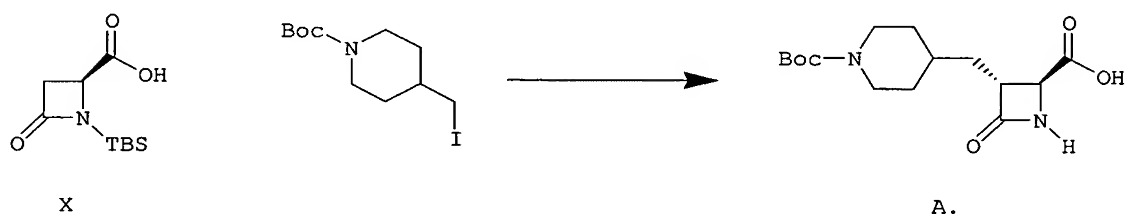
The title compound was prepared according to the following reaction scheme and as described below.



55 (Example 5 Compound)

Preparation of Example 5 Compound

1. Preparation of 51

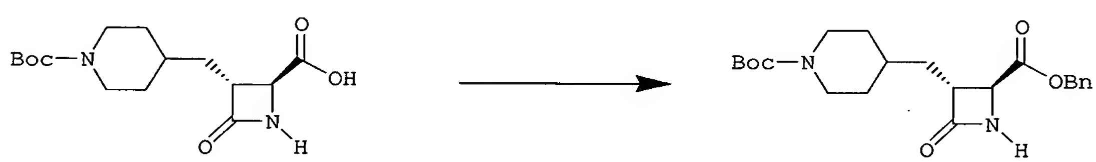


A. To a solution of iPr_2NH (6.42 ml, 45.8 mmol) in THF (15 ml) at 0 °C was added nBuLi (1.6 M, 28 ml, 45 mmol). After stirring at room temperature for 1 hour, the reaction mixture was cooled to –78 °C and treated dropwise over 5 minutes with a solution of **X** (5 g, 21.8 mmol in 15 ml THF). The reaction mixture was then warmed to –20 °C and a slurry formed. THF (15 ml) was added to loosen the slurry and the slurry was stirred vigorously for 2.5 hour at –20 °C. A solution of N-Boc-4-(iodomethyl)piperidine (10.63 g, 32.7 mmol in 15 ml THF) was added dropwise over

3 minutes and the resulting solution was stirred at –20 °C for 18 hours. The reaction mixture was partitioned between EtOAc (200 ml) and water (200 ml). After mixing and separation, the organic phase was extracted once more with water (150 ml). The combined water layers were then washed with EtOAc (2x200ml). The aqueous phase was diluted with EtOAc (200ml) and with rapid stirring brought to pH 2-3 with portionwise addition of solid $KHSO_4$. The EtOAc layer was removed and the aqueous layer was extracted with EtOAc (3x200 ml). The EtOAc extracts from the acidified aqueous layer were combined, dried over Na_2SO_4, filtered and concentrated.

The residue was taken up in THF (30 ml), treated with TBAF (1.0 M THF, 22 ml) and stirred at room temperature for 2 hours. The reaction mixture was partitioned between EtOAc and 0.5N KHSO4. The aqueous phase was then extracted with EtOAc (4x). The combined EtOAc extracts were dried over MgSO4, filtered and concentrated to give Part A compound (2.8 g, 42%).

1H-NMR (400 MHz, CDCl3) δ 8-9 (bs, 1H), 6.82 (s, 1H), 4.1 (m, 2H), 3.88 (d, 1H, *j* = 2.47), 3.36 (m, 1H), 2.67 (m, 2H), 1.6-1.9 (m, 6H), 1.43 (s, 9H), 1.1 (m, 1H).



A.　　　　　　51

B. $NaHCO_3$ (0.58g, 6.92 mmol) was added to a stirred solution of crude Part A compound (1.08 g, 3.46 mmol) and benzylbromide (2.06 ml, 17.30 mmol) in DMF (10 ml) at room temperature. After 20 h the reaction mixture was partitioned between ethylacetate and water. The organic phase was isolated, washed with saturated NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography to afford 0.77g of compound 51.

2. Preparation of 52

H_2O (2.0 mL) was added to compound 51 (20 mg, 0.043 mmol). MeOH was added until all of 51 dissolved. 1N HCl (45μL, 0.045 mmol) was added. After 5 min of stirring the solution was conc. to remove MeOH and lyophilized. 18 mg (84%) of 52 was obtained. IR (KBr) : 1788 cm^{-1}

3. Preparation of 53

Compound 51 (244 mg, 0.606 mmol) and Compound 52 (212mg, 0.727 mmol) were dissolved in CH_2Cl_2 (3.0 mL). TEA (127 uL, 0.909 mmol) was added followed by DMAP (15 mg, 0.121 mmol). After 24 hr the reaction mixture was conc. and the residue was partitioned between EtOAc and H_2O. The organic phase was isolated, washed with 1N HCl, sat. NaCl, dried ($MgSO_4$), and conc. The residue was purified by silica gel chromatography to afford 348 mg (87%) of 53.

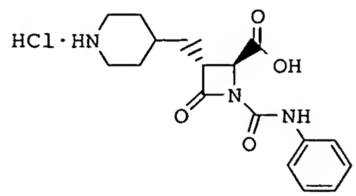
4. Preparation of 54

Compound 53 (138 mg, 0.210 mmol) was dissolved in EtOAc (0.40 mL). 10% Pd/C (15 mg) was added and a H_2 atmosphere was introduced via balloon. After 1 hr the reaction mixture was diluted with EtOAc and filtered. The filtrate was conc. to afford 122 mg (100%) of 54.

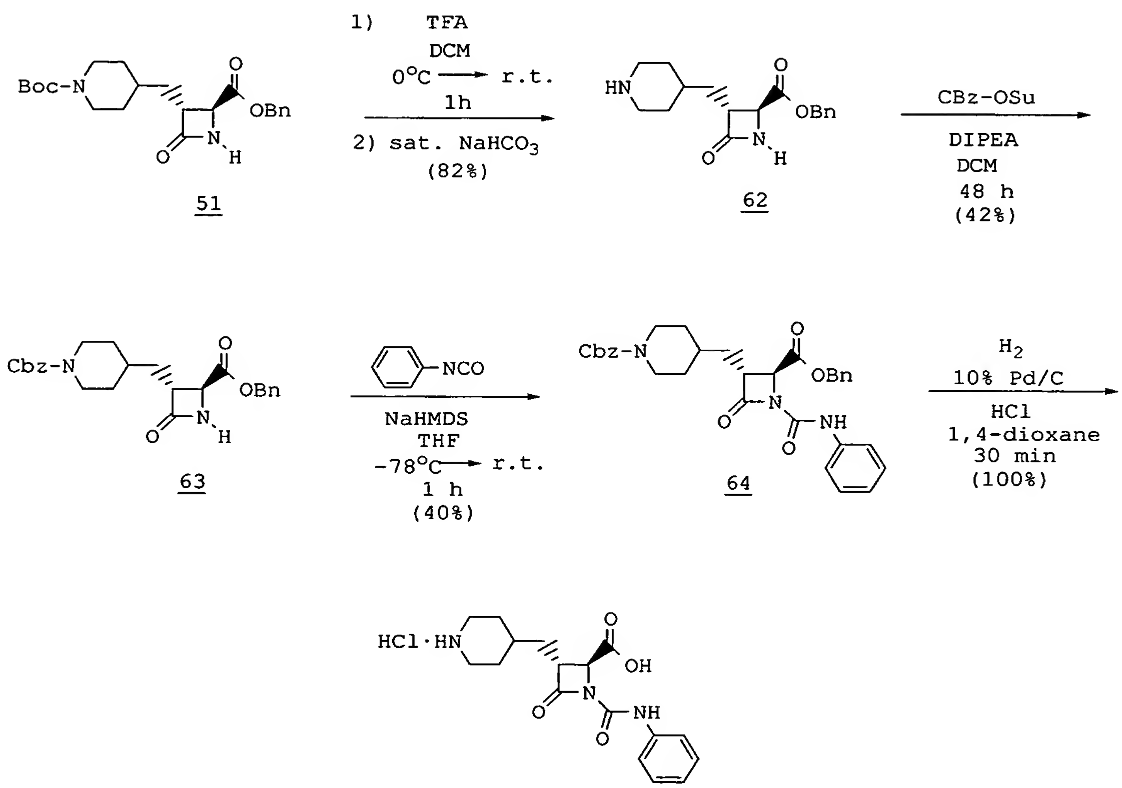
5. Preparation of 55 (Example 55 Compound)

TFA (0.40 mL) was added dropwise to a stirred solution of compound 54 (86 mg, 0.152 mmol) in CH_2Cl_2 (1.20 mL) at 0°C. The reaction mixture was then stirred at room temp. After 1 hr the reaction mixture was conc. and placed under vacuum. The crude product was dissolved in H_2O and placed on top of a column of cleaned PVP resin. The column was eluted with H_2O. Fractions containing product were combined and lyophilized. 63 mg (89%) of 55 (Example 5 compound) was obtained. LR-MS(ESI); (M+H) calc'd = 467, found = 467.

EXAMPLE 6



The title compound was prepared according to the following reaction scheme as described below.



65 (Example 6 Compound)

Preparation of Example 6 Compound

1. Preparation of 62

TFA (0.40 mL) was added dropwise to a stirred solution of compound 51 prepared in Example 5 (130 mg, 0.323 mmol) in CH_2Cl_2 (1.20 mL) at 0°C. The

reaction mixture was then stirred at room temp. After 1 hr the reaction mixture was conc. and placed under vacuum. The crude product was stirred with $CHCl_3$ and sat. $NaHCO_3$. The organic phase was isolated, dried ($MgSO_4$), and conc. 80 mg (82%) of 62 was obtained.

2. Preparation of 63

N-(Benzyloxycarbonyloxy)succinimide (61 mg, 0.243 mmol) was added to a stirred solution of compound 62 (70 mg, 0.171 mmol) in CH_2Cl_2 (1.00 mL). After 24 hr DIPEA (40 μL, 0.232 mmol) was added. After 24 hr the reaction mixture was diluted with EtOAc, washed with 1N HCl, sat. $NaHCO_3$ and sat. NaCl. dried ($MgSO_4$), and conc. The crude product was purified by silica gel chromatography to give 42 mg (42%) of compound 63.

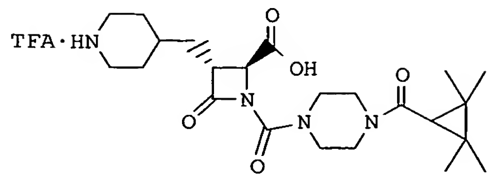
3. Preparation of 64

A 1.0M THF solution of NaHMDS (115 μL, 0.115 mmol) was added dropwise to a stirred solution of compound 63 (42 mg, 0.096 mmol) in THF (0.70 mL) at -78°C. After 25 min of stirring phenyl isocyanate (12 μL, 0.106 mmol) was added dropwise. The temp. was slowly raised to room temp. After 1 h the reaction mixture was cooled to 0°C quenched by addition of 5% $KHSO_4$.The solution was partitioned between EtOAc and water. The organic phase was isolated, washed with sat. NaCl, dried ($MgSO_4$), and conc. The residue was purified by silica gel chromatography to afford 21 mg (40%) of compound 64.

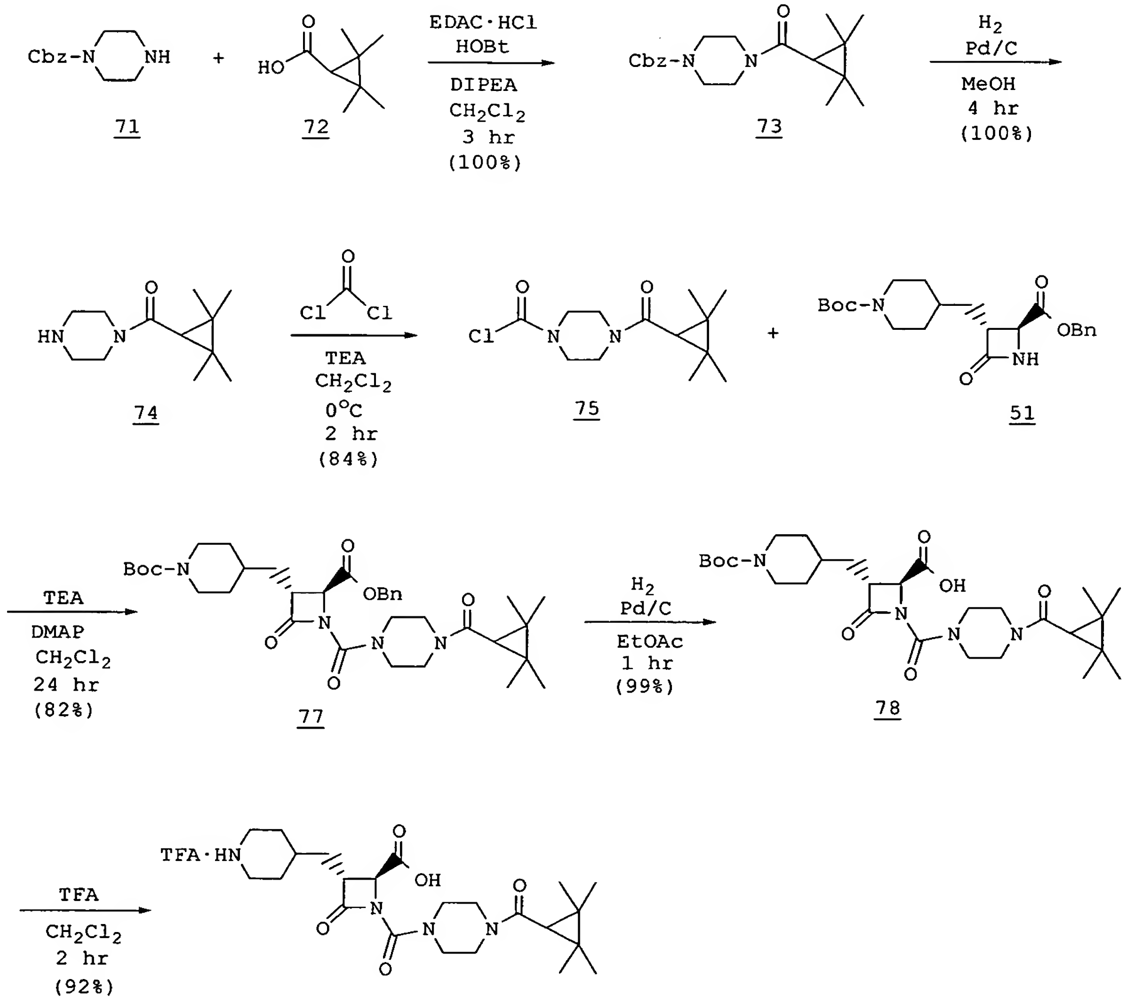
4. Preparation of 65 (Example 6 Compound)

Compound 64 (21 mg, 0.038 mmol) was dissolved in 1,4 - dioxane (0.40 mL) and water (0.04 mL). 1N HCl (40 μL, 0.040 mmol) was added followed by 10% Pd/C (5 mg). A H_2 atmosphere was introduced via balloon. After 40 min of stirring at room temp. the reaction mixture was diluted with H_2O : 1,4 - dioxane; 1:1 and filtered. The filtrate was lyophilized to afford 15 mg (100%) of 65 (Example 6 compound). IR (KBr) : 1784 cm^{-1}

EXAMPLE 7



The title compound was prepared according to the following reaction scheme and as described below.



79 (Example 7 Compound)

Preparation of Example 7 Compound

1. Preparation of 73

EDAC·HCl (0.65 g, 3.37 mmol) was added to a stirred solution of compound 71 (0.62 g, 2.81 mmol), compound 72 (0.40 g, 2.81 mmol), HOBt (0.46 g, 3.37 mmol), and DIPEA (0.69 mL, 3.93 mmol) in CH_2Cl_2 (12 mL) at room temp. After 3 hr the reaction mixture was conc. and the residue was partitioned between EtOAc and 1N HCl. The organic phase was isolated, washed with 1N HCl, H_2O, sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$), and conc. to give 0.97 g (100%) of compound 73.

2. Preparation of 74

Compound 73 (0.97 g, 2.82 mmol) was dissolved in MeOH (10 mL). 10% Pd/C (100 mg) was added and a H_2 atmosphere was introduced via balloon. After 4 hr the reaction mixture was filtered. The filtrate was conc. to afford 0.59 g (100%) of compound 74.

3. Preparation of 75

Phosgene(20% in toluene) (5.23 mL, 9.84 mmol) was added to a stirred solution of compound 74 (0.59 g, 2.81 mmol) and TEA (0.47 mL, 3.37 mmol) in CH_2Cl_2 (10 mL) at 0°C. After 2 hr the reaction mixture was conc. and the residue was triturated with Et_2O. The solution was filtered and the filtrate was conc. The crude product was purified by silica gel chromatography to give 0.64 g (84%) of compound 75.

4. Preparation of 77

Compound 75 (50 mg, 0.185 mmol) and compound 51 (prepared as described in Example 5) (62 mg, 0.154 mmol) were dissolved in CH_2Cl_2 (0.77 mL). TEA (30 uL, 0.216 mmol) was added followed by DMAP (4.0 mg, 0.031 mmol). After 24 hr the reaction mixture was conc. and the residue was partitioned between EtOAc and 1N HCl. The organic phase was isolated, washed with 1N HCl, dried ($MgSO_4$), and conc. The crude product was purified by silica gel chromatography to give 80 mg (82%) of compound 77.

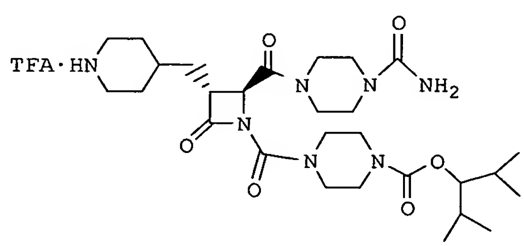
5. Preparation of 78

Compound 77 (80 mg, 0.125 mmol) was dissolved in EtOAc (1 mL). 10% Pd/C (10 mg) was added and a H_2 atmosphere was introduced via balloon. After 1 hr the reaction mixture was diluted with EtOAc and filtered. The filtrate was conc. to afford 68 mg (99%) of compound 78.

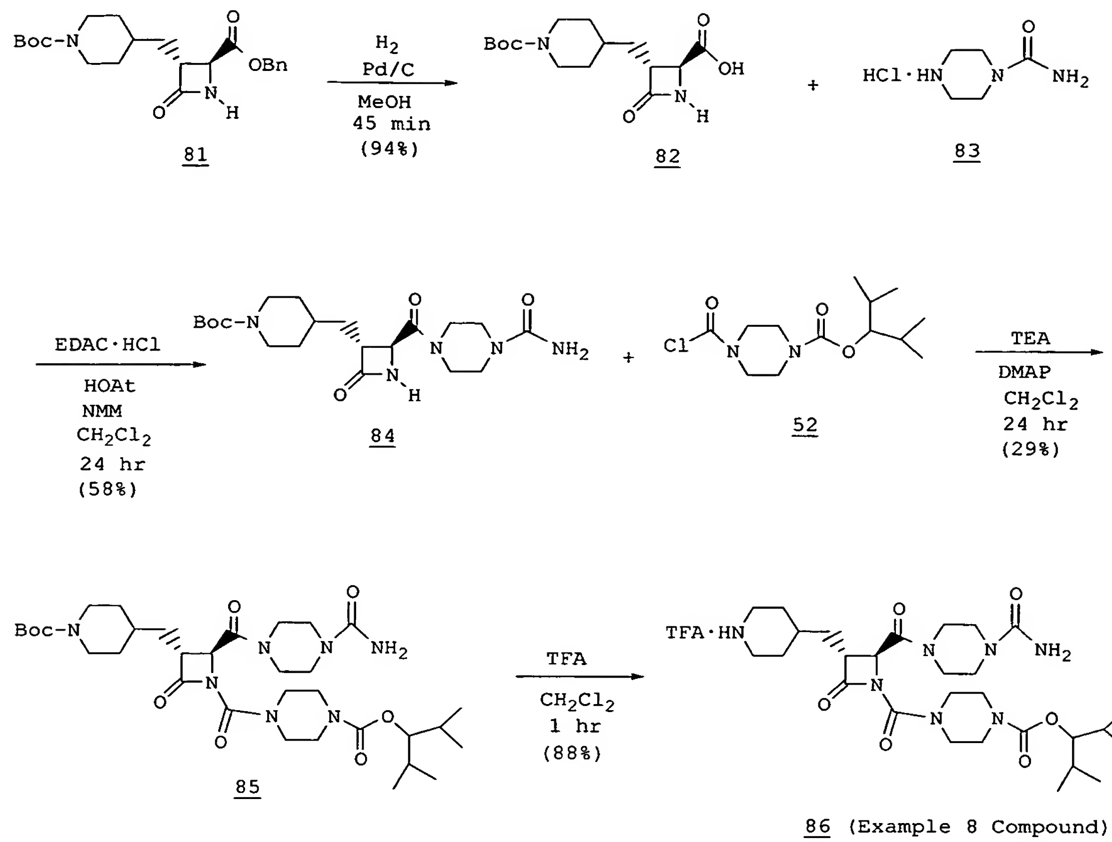
6. Preparation of 79 (Example 7 Compound)

TFA (0.20 mL) was added dropwise to a stirred solution of compound 78 (68 mg, 0.124 mmol) in CH_2Cl_2 (0.60 mL) at 0°C. The reaction mixture was then stirred at room temp. After 2 hr the reaction mixture was conc. and placed under vacuum. The crude product was dissolved in H_2O and lyophilized. 64 mg (92%) of 79 (Example 7 compound) was obtained. . LR-MS(ESI); (M+H) calc'd = 449, found = 449.

EXAMPLE 8



The title compound was prepared according to the following reaction sequence and as described below.



Preparation of Example 8 Compound

1. Preparation of Compound 82

Example 5 compound 51 (210 mg, 0.522 mmol) was dissolved in MeOH (2.0 mL). 10% Pd/C (21 mg) was added and a H_2 atmosphere was introduced via balloon. After 45 min the reaction mixture was filtered. The filtrate was conc. to afford 154 mg (94%) of compound 82.

2. Preparation of Compound 83

This compound is prepared in Example 74 of U.S. Patent No. 6,335,324.

3. Preparation of Compound 84

EDAC·HCl (44 mg, 0.229 mmol) was added to a stirred solution of compound 82 (55 mg, 0.176 mmol), compound 83 (35 mg, 0.211 mmol), HOAt (31 mg, 0.229 mmol), and NMM (48 μL, 0.440 mmol) in CH_2Cl_2 (0.70 mL) at room temp. After 24

hr the reaction mixture was conc. and the residue was partitioned between EtOAc and 5% $KHSO_4$.The organic phase was isolated, washed with sat. $NaHCO_3$, sat. NaCl, dried ($MgSO_4$), and conc. to give 43 mg (58%) of compound 84.

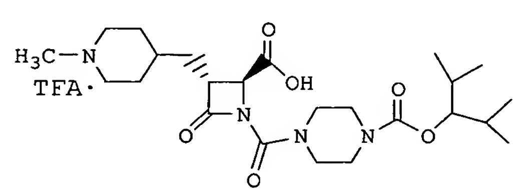
4. Preparation of Compound 85

Compound 84 (41 mg, 0.097 mmol) and Example 5 compound 52 (37 mg, 0.126 mmol) were dissolved in CH_2Cl_2 (0.50 mL). TEA (20 uL, 0.145 mmol) was added followed by DMAP (2.0 mg, 0.019 mmol). After 24 hr the reaction mixture was conc. and the residue was partitioned between EtOAc and 5% $KHSO_4$.The organic phase was isolated, washed with sat. NaCl, dried ($MgSO_4$), and conc. The crude product was purified by silica gel chromatography to afford 19 mg (29%) of compound 85.

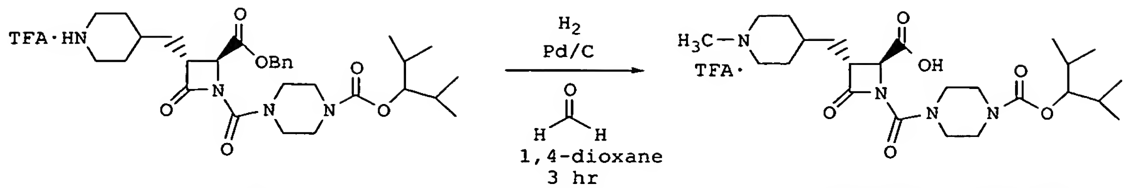
5. Preparation of Compound 86 (Example 8 Compound)

TFA (0.125 mL) was added dropwise to a stirred solution of compound 86 (19 mg, 0.028 mmol) in CH_2Cl_2 (0.375 mL) at 0°C. The reaction mixture was then stirred at room temp. After 1 hr the reaction mixture was conc. and placed under vacuum. The crude product was dissolved in H_2O and lyophilized. 17 mg (88%) of 86 (Example 8 compound) was obtained. IR (KBr) : 1784 cm^{-1}

EXAMPLE 9



The title compound was prepared according to the following reaction scheme and as described below.



91   92 (Example 9 Compound)

Preparation of Example 9 Compound

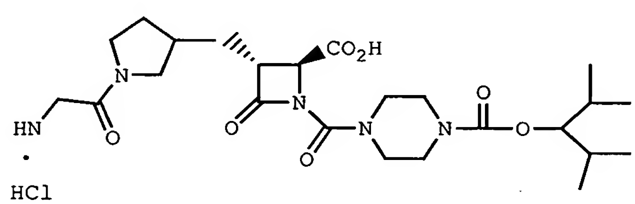
1. Preparation of Compound 91

See Example 11 Part 1 for preparation.

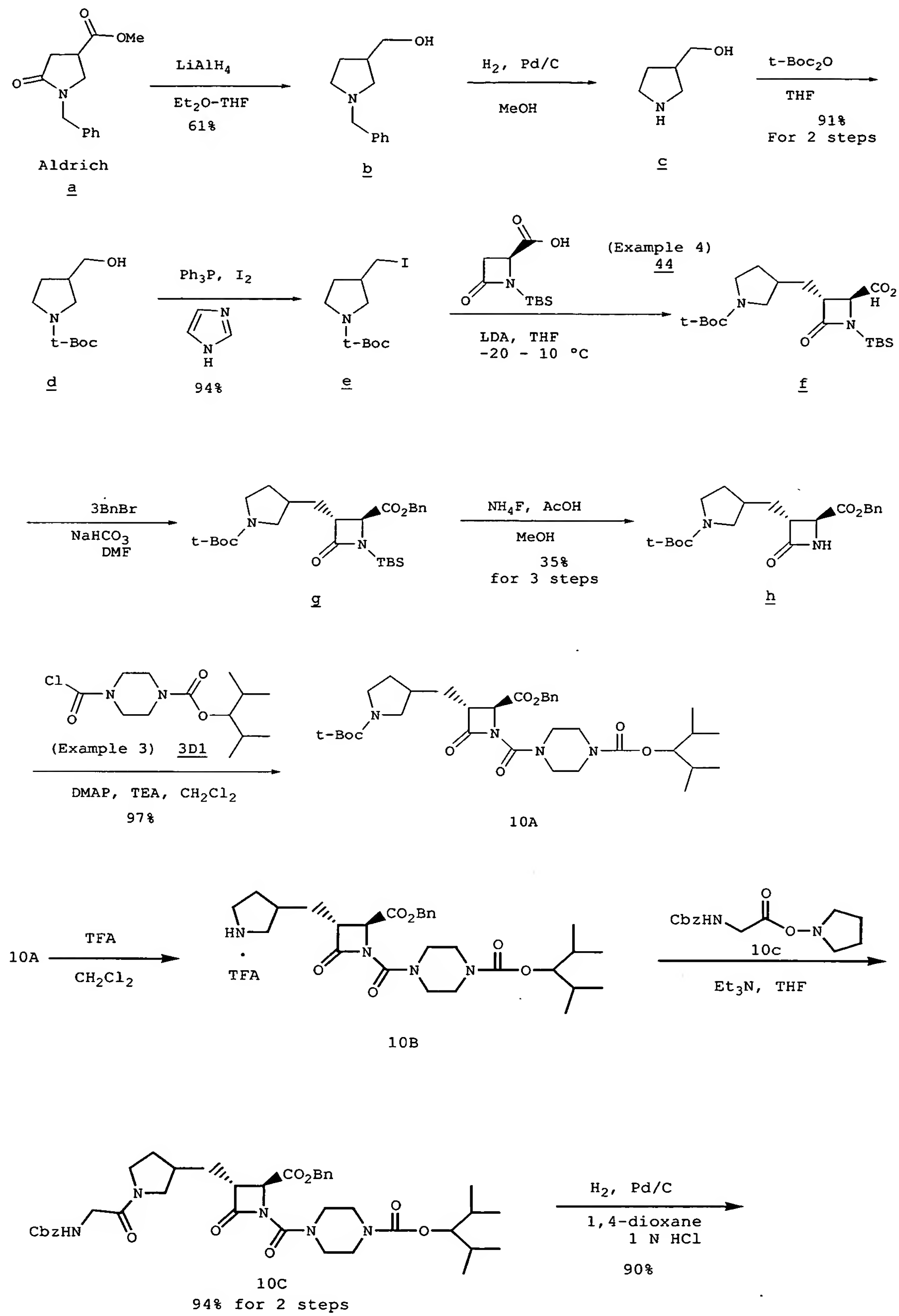
2. Preparation of Compound 92 (Example 9 Compound)

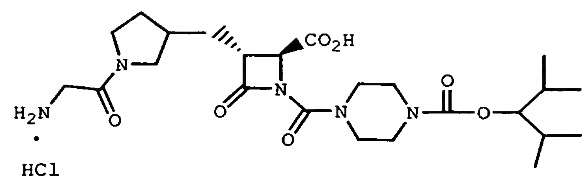
Compound 91 (86 mg, 0.128 mmol) was dissolved in 1,4 - dioxane (0.8 mL). Formaldehyde(37 wt % in H_2O) (44 uL) was added followed by 10% Pd/C (15 mg) A H_2 atmosphere was introduced via balloon. After 3 hr the reaction mixture was diluted with H_2O : 1,4 - dioxane; 1:1, filtered, and the filtrate was lyophilized. The crude product was purified by PREP HPLC to afford 22 mg (29%) of compound 92 (Example 9 compound). IR (KBr) : 1787 cm^{-1}

EXAMPLE 10



The title compound was prepared according to the following reaction sequence and as described below.





10D
1 : 1 mixture of diastereomers

Preparation of Example 10 Compound

1. Preparation of Compound 10A

A. Preparation of Compound b

Compound b was prepared by a similar procedure to Wu's (J. Org. Chem. 1961, 1519.) except using THF to dissolve methyl 1-benzyl-5-oxo-3pyrrolidinecarboxylate:

A solution of methyl 1-benzyl-5-oxo-3pyrrolidinecarboxylate (a) (8.00g, 34.30mmol) in 10 mL of anhydrous THF was slowly added to a slurry of powdered lithium aluminum hydride (1.82g, 48.01 mmol) in 30 mL of absolute ether. The addition was made over a period of 0.5 hour with efficient stirring so as to maintain a moderate reflux rate. When the addition was complete, refluxing and stirring was continued for 2 hours, after which the reaction mixture was left at room temperature. The mixture was quenched with 3 mL of water, and stirred for 2 hours. The white precipitate was filtered and washed with 2x30 mL of ether. The solid was extracted with Soxhlet type apparatus in EtOH for 8 hours. Th EtOH was removed. The residue was washed with Et_2O (3x20 mL). The Et_2O solutions were combined, dried over $MgSO_4$, and concentrated. The residue was distilled under vacuum. The fraction at 137-145 °C /1 mmHg was collected to give compound b (4.0 g) as a colorless oil.

B. Preparation of Compound c and Compound d

To a solution of the amino alcohol b (1.50g, 7.84 mmol) in 100 mL of MeOH was added Pd/C (400 mg). The mixture was stirred for 8 hours under H_2 atomphere. MeOH was removed to give residue c as colorless oil. The residue c was dissolved in 50 mL of THF. t-Boc_2O (2.50 g, 11.76 mmol) was added The solution was stirred for

8 hours and THF was removed. The residue was partitioned between ether (200 mL) and 0.25 M $KHSO_4$ (100mL). The ether layer was washed with sat. $NaHCO_3$ (20 mL) and brine, dried over $MgSO_4$, and concentrated. The residue was purified with silica gel chromatography (CH_2Cl_2 : MeOH = 10: 1, Rf = 0.35) to provide d (1.40 g) as a colorless oil. MS 202.4 $(M+H)^+$.

C. Preparation of Compound e

Triphenyl phosphine (2.89 g, 11.00 mmol) was dissolved in 25 mL of CH_2Cl_2. Imidazole (0.75 g, 11.00 mmol) was added followed by iodine (2.79 g, 11.00 mmol). The solution of compound d in 5 mL of CH_2Cl_2 was slowly added. The reaction mixture was stirred for at room temperature for 2 hours, and then filtered. The filtrate was concentrated. The residue was triturated with EtOAc, The EtOAc solution was washed with 5% NaS_2O_3 and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel chromatography (ethyl acetate : hexane = 6 : 1, Rf = 0.25) to afford compound e (2.30 g) as a colorless oil. MS: 312.1 $(M+H)^+$.

D. Preparation of Compound f

To a solution of diisopropylamine (0.68 mL, 4.82 mmol) in 5 mL of THF was added BuLi (1.6 M, 2.88 mL, 4.62 mmol) at –15 °C. The solution was cooled to –78 °C and stirred for 20 minutes. A solution of β-lactam 44 (from Example 4) (500 mg, 2.20 mmol) in 2 mL of THF was added dropwise. The solution was warmed to –20 °C to –10 °C and stirred at this temperature for 30 minutes. Then a solution of compound e (1.03 g, 3.30mmol) in 3 mL of THF was added. The reaction mixture was stirred for 8 hours and then quenched with 5% $KHSO_4$ until PH = 3-4. The aqueous solution was extracted with EtOAc (3x20 mL). Organic extracts were combined, washed with brine, and concentrated. The residue was taken up with 60 mL of ether and the solution was extracted with sat. $NaHCO_3$ solution (3x20 mL). The basic aqueous layers were washed with ether (20 mL), cooled to 0 °C, acidified with 10% $KHSO_4$ until PH = 3-4, extracted with EtOAc (3x20mL). The extracts were washed with brine, dried over $MgSO_4$, and concentrated to provide compound f as a colorless oil (0.60 g). MS 413.3 $(M+H)^+$.

E. Preparation of Compound g

Compound f (0.60 g 1.45 mmol) was dissolved in 10 mL of DMF. $NaHCO_3$ (244 mg, 2.90 mmol) followed by benzyl bromide. The reaction mixture was stirred overnight at room temperature, then partitioned between water (20 mL) and EtOAc (60mL). The organic layer was washed with brine, dried over MgSO4, and concentrated to give crude compound g as colorless oil.

F. Preparation of Compound h

The crude compound g was dissolved in 10 mL of methanol. Acetic acid (0.25 mL, 4.35 mmol) and a solution of NH_4F (0.5 M, 2.90 mL, 1.45 mmol) in methanol was added. The solution was stirred for 1hour. The solvents were replaced with 60 mL of CH_2Cl_2, washed with sat. $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 1 : 1, Rf = 0.12) to afford compound h (300 mg) as a white solid.

G. Preparation of Compound 10A

To a solution of ester h (260 mg, 0.67 mmol) in 5 mL of CH_2Cl_2 was added triethyl amine (0.11 mL, 0.81 mmol), acid chloride (compound 3D1 in Example 3) (233 mg, 0.81 mmol), and DMAP (4.0 mg, 0.034 mmol). The solution was stirred for 3 hour. The solvent was removed. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 2 : 1, Rf = 0.26) to afford compound 10A (417 mg) as a colorless oil.

2. Preparation of Compound 10B

Compound 10A (85 mg, 0.13 mmol) was dissolved in 0.8 mL of CH_2Cl_2. The solution was cooled to 0 °C and TFA (0.2 mL) was added dropwise. The ice-bath was removed The mixture was stirred at room temperature for 1 hour. The solvents were removed under vacuum to generate crude compound 10B as colorless oil.

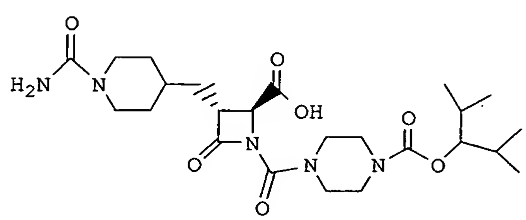
3. Preparation of Compound 10C

Compound 10B (0.13 mmol) was dissolved in 1 mL of THF. Cbz-Gly-OSu (10c) (50 mg, 0.16 mmol) was added followed by triethyl amine. The reaction mixture was stirred overnight at room temperature, diluted with ethyl acetate(50 mL), washed with 5% $KHSO_4$, Sat. $NaHCO_3$ solution, and brine, dried with $MgSO_4$ and concentrated. The residue was purified with silica gel chromatography (ethyl acetate : hexane = 2 : 3 to 1 : 2) to afford compound 10C (90 mg) as a colorless oil.

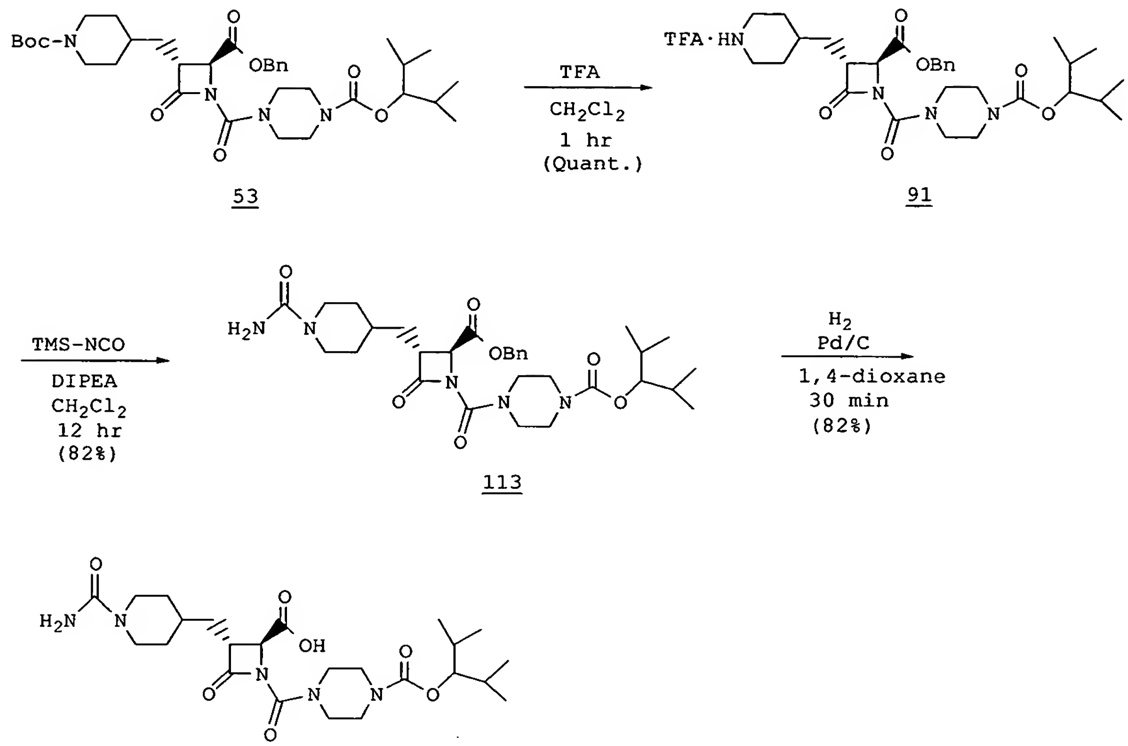
4. Preparation of Compound 10D

A mixture of compound 10C (68 mg, 0.092 mmol), Pd/C (10%, 15 mg) and 1 N HCl (92 µL, 0.092 mmol) in 1,4-dioxane (1 mL) was stirred under hydrogen atmosphere (hydrogen balloon) at room temperature for 8 hours. Analytical HPLC indicated the completion of the reaction. The reaction mixture was diluted 2 mL of water, filtered through a celite pad, and lyophilized to give title compound 10D (Example 10 compound) (45 mg) as a white powder. Purity by anal HPLC: 98%; MS: 510.3 $(M+H)^+$, 508.2 $(M-H)^-$; IR: (KBr pellet) υ 1787 cm^{-1}.

EXAMPLE 11



The title compound was prepared according to the following reaction sequence and as described below.



114 (Example 11 Compound)

Preparation of Example 11 Compound

1. **Preparation of Compound 91**

TFA (0.70 mL) was added dropwise to a stirred solution of compound 53 (prepared in Example 5) (172 mg, 0.262 mmol) in CH_2Cl_2 (2.1 mL) at 0°C. The reaction mixture was then stirred at room temp. After 1 hr the reaction mixture was conc. and placed under vacuum. 176 mg (100%) of compound 112 was obtained.

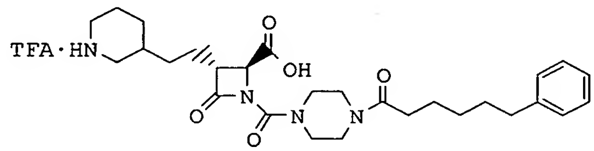
2. **Preparation of Compound 113**

TMS-NCO (25 uL, 0.188 mmol) was added to a stirred solution of compound 91 (67 mg, 0.100 mmol) and DIPEA (44 uL, 0.250 mmol) in CH_2Cl_2 (1 mL) at 0°C. The reaction mixture was then stirred at room temp. After 12 hr the reaction mixture was partitioned between CH_2Cl_2 and 5% $KHSO_4$.The organic phase was isolated, dried ($MgSO_4$), and conc. The crude product was purified by silica gel chromatography to give 49 mg (82%) of compound 113.

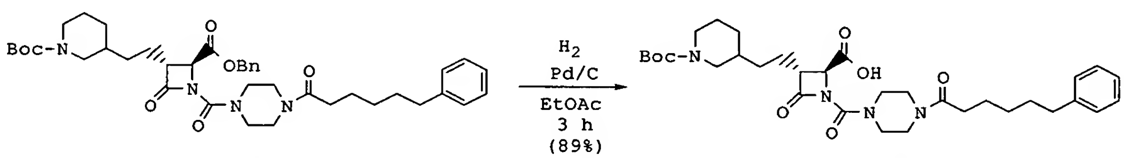
3. Preparation of Compound 114

Compound 113 (49 mg, 0.082 mmol) was dissolved in 1,4 - dioxane (0.5 mL). 10% Pd/C (10 mg) was added and a H_2 atmosphere was introduced via balloon. After 30 min of stirring at room temp. the reaction mixture was diluted with 1,4 – dioxane and filtered. The filtrate was lyophilized to afford 34 mg (82%) of compound 114 (Example 11 compound). IR (KBr) : 1786 cm^{-1}

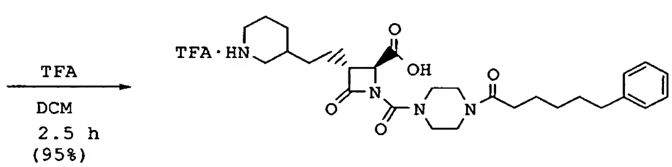
EXAMPLE 12



The title compound was prepared according to the following reaction sequence and as described below.



121 122



123 (Example 12 Compound)

Preparation of Example 12 Compound

1. Preparation of Compound 121

This compound is prepared as described in U.S. Patent No. 6,335,324, Example 202 Part h.

2. Preparation of Compound 122

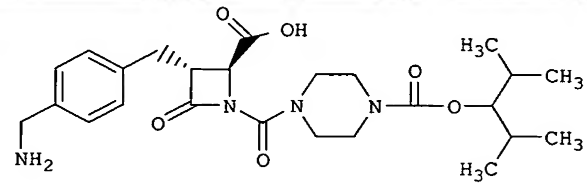
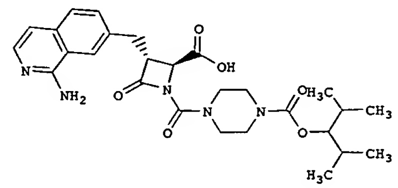
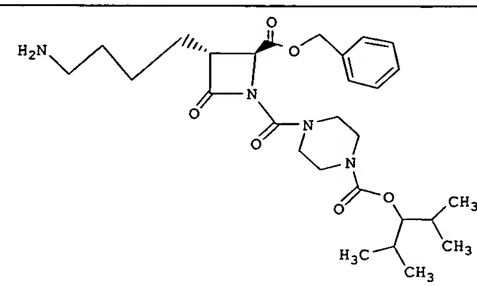
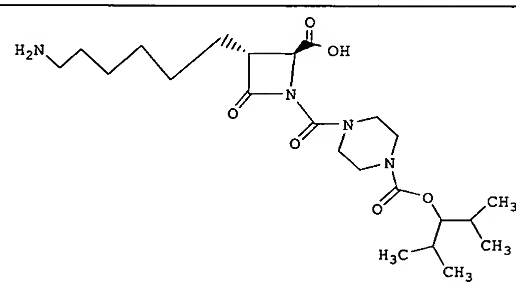
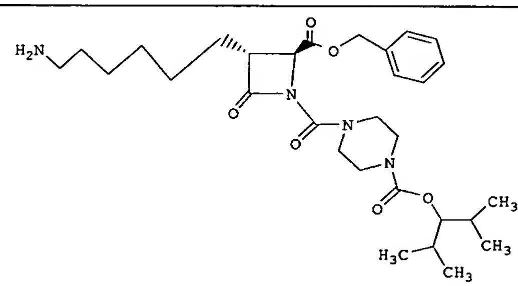
Compound 121 (84 mg, 0.120 mmol) was dissolved in EtOAc (1.50 mL). 10% Pd/C (12 mg) was added and a H_2 atmosphere was introduced via balloon. After 3 hr the reaction mixture was diluted with EtOAc and filtered. The filtrate was conc. to afford 65 mg (89%) of compound 122.

3. Preparation of Compound 123 (Example 12 Compound)

TFA (0.25 mL) was added dropwise to a stirred solution of compound 122 (65 mg, 0.106 mmol) in CH_2Cl_2 (0.75 mL) at 0°C. The reaction mixture was then stirred at room temp. After 2.5 hr the reaction mixture was conc. and placed under vacuum. The crude product was dissolved in H_2O (1.0 mL) and 1,4-dioxane (3.0 mL) and lyophilized. 63 mg (95%) of compound 123 (Example 12 compound) was obtained. LR-MS(ESI); (M+H) calc'd =513, found =513.

Following the procedures set out in Examples 1 to 12 and in the reaction schemes, the following compounds were prepared.

EXAMPLES 13 TO 17

Example No.	Structure
13	
14	
15	
16	
17	

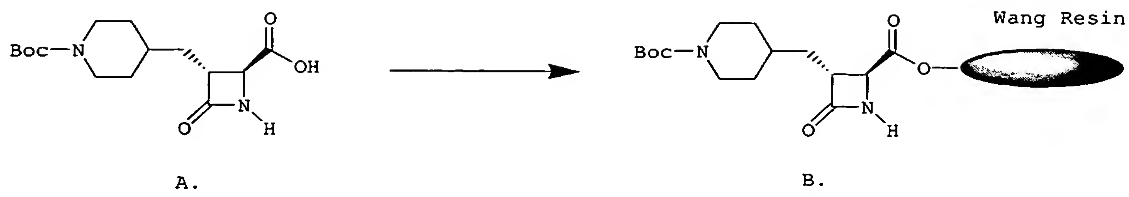
EXAMPLE 18

2B1 A.

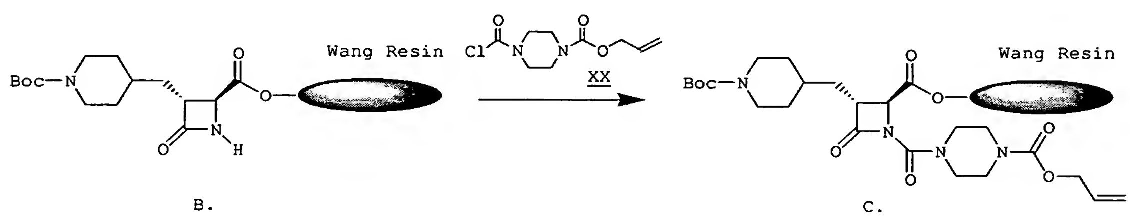
A. To a solution of iPr_2NH (6.42 ml, 45.8 mmol) in THF (15 ml) at 0 °C was added nBuLi (1.6 M, 28 ml, 45 mmol). After stirring at room temperature for 1 hour, the reaction mixture was cooled to –78 °C and treated dropwise over 5 minutes with a solution of 2B1 (5 g, 21.8 mmol in 15 ml THF). The reaction mixture was then warmed to –20 °C and a slurry formed. THF (15 ml) was added to loosen the slurry and the slurry was stirred vigorously for 2.5 hour at –20 °C. A solution of N-Boc-4-(iodomethyl)piperidine (10.63 g, 32.7 mmol in 15 ml THF) was added dropwise over 3 minutes and the resulting solution was stirred at –20 °C for 18 hours. The reaction mixture was partitioned between EtOAc (200 ml) and water (200 ml). After mixing and separation, the organic phase was extracted once more with water (150 ml). The combined water layers were then washed with EtOAc (2x200ml). The aqueous phase was diluted with EtOAc (200ml) and with rapid stirring brought to pH 2-3 with portionwise addition of solid $KHSO_4$. The EtOAc layer was removed and the aqueous layer was extracted with EtOAc (3x200 ml). The EtOAc extracts from the acidified aqueous layer were combined, dried over Na_2SO_4, filtered and concentrated.

The residue was taken up in THF (30 ml), treated with TBAF (1.0 M THF, 22 ml) and stirred at room temperature for 2 hours. The reaction mixture was partitioned between EtOAc and 0.5N KHSO4. The aqueous phase was then extracted with EtOAc (4x). The combined EtOAc extracts were dried over MgSO4, filtered and concentrated to give Part A compound (2.8 g, 42%).

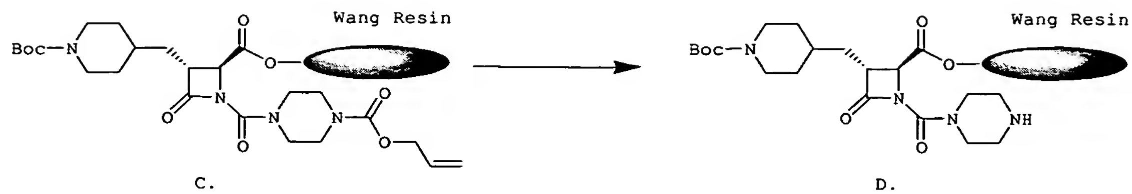
1H-NMR (400 MHz, CDCl3) δ 8-9 (bs, 1H), 6.82 (s, 1H), 4.1 (m, 2H), 3.88 (d, 1H, *j* = 2.47), 3.36 (m, 1H), 2.67 (m, 2H), 1.6-1.9 (m, 6H), 1.43 (s, 9H), 1.1 (m, 1H).



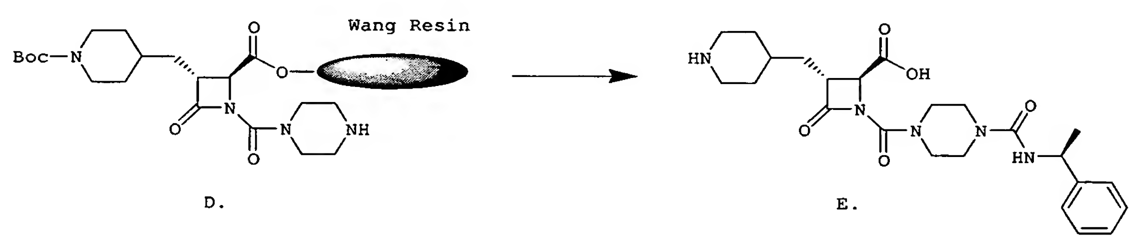
B. To a suspension of Part A compound (4.1g, 13.14 mmol) in DCM:THF (1:1, 100 ml) at room temperature was added MSNT (3.89g, 13.14 mmol) followed by *N*-methylimidazole (2.7 ml). The reaction mixture was stirred for 3 to 5 minutes until all materials dissolved. The reaction mixture was then added to DCM rinsed Wang Resin (12 g dry weight, 0.7 mmol/g theoretical load capacity) and the reaction was aggitated for 48 hours at RT. The resin was washed with THF (100 ml) and the eluent was collected and saved. The resin was then washed with DMF (4x100 ml), THF (4x100 ml), DCM (4x100 ml) and Et_2O (4x100 ml). The resin was dried under vacuum for 24 hours to give resin bound Part B compound (14.8 g).



C. To a suspension of Part B compound resin (14.8 g, ~8.4 mmol load) in DCM (65 ml) was added carbamoyl chloride XX (3.9 g, 16.8 mmol), Et_3N (11 ml) and DMAP (3.8 g). The reaction was aggitated at room temperature for 24 hours. The resin was drained and then washed with DMF (4x75 ml), THF (4x75 ml), DCM (4x75 ml) and Et_2O (4x75 ml). The resin was then dried under vacuum overnight to give Part C compound resin (15.25 g, 96% purity determined by HPLC of a 15 mg sample treated with 20% TFA/DCM for 1.5 hours. HPLC conditions - Phenomenex-Prime S5 C18 4.6x50 mm, 4 min gradient, 0 to 100% B solvent, 1 minute hold, 4 ml/min, A = 10% MeOH/Water + 0.2% H_3PO_4, B = 90%MeOH/Water + 0.2% H_3PO_4. Retention time 2.15 minutes).

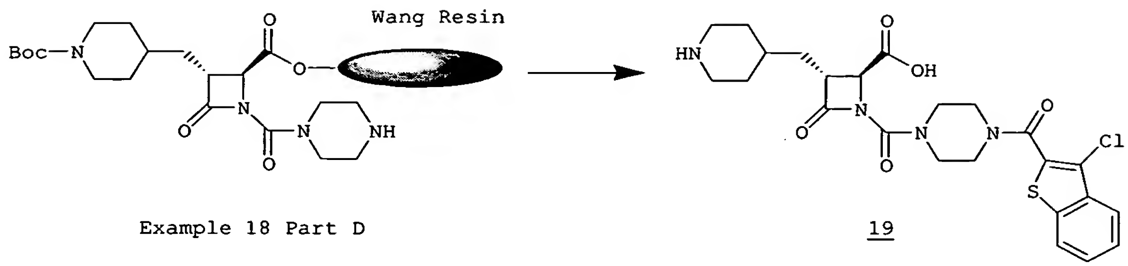


D. To a suspension of Part C compound resin (15.25 g, ~8.4 mmol load) in DCM (75 ml) at room temperature was added $PhSiH_3$ (15.5 ml, 126 mmol) followed by $Pd(PPh_3)_4$ (485 mg, 0.42 mmol). The reaction was aggitated for 6 hours at room temperature. The resin was then washed with DMF (4x100 ml), 30% MeOH/DCM (4x100 ml), DCM (4x100 ml) and Et_2O (3x100 ml). The resin was vacuum dried overnight to give Part D compound resin (14.2 g, 95% purity determined by HPLC of a 42 mg sample treated with 20% TFA/DCM for 1.5 hours which gave 0.29 mmole of product. HPLC conditions - Phenomenex-Prime S5 C18 4.6x50 mm, 4 min gradient, 0 to 100% B solvent, 1 minute hold, 4 ml/min, A = 10% MeOH/Water + 0.2% H_3PO_4, B = 90%MeOH/Water + 0.2% H_3PO_4. Retention time 0.243 minutes).



E. To S-(-)-α-methylbenzylisocycante (0.072 mmol) was added 1ml of a solution comprised of DCM (30 ml), Et3N (401 μl) and DMAP (87 mg). After aggitating to dissolve all materials, Part D compound resin (35 mg) was added and the reaction was aggitated for 36 hours. The resin was washed with DMF:DMSO (1:1, 4x5 ml) and DCM (4x5 ml). The resin was then treated with 20% TFA/DCM (1.2 ml) for 2 hours. Eluent was collected and solvent reduced to provide product E (12.2 mg); 87% purity by LCMS, (M+H)+ = 472.36.

EXAMPLE 19



Example 18 Part D

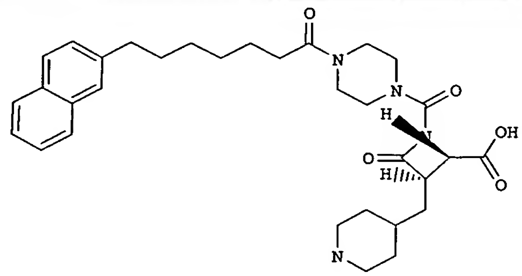
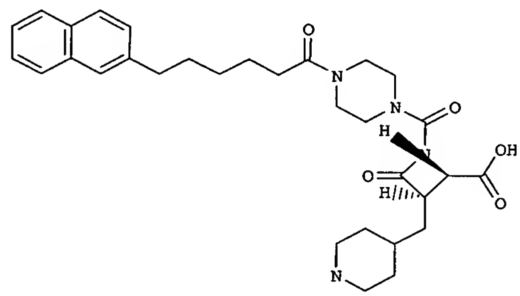
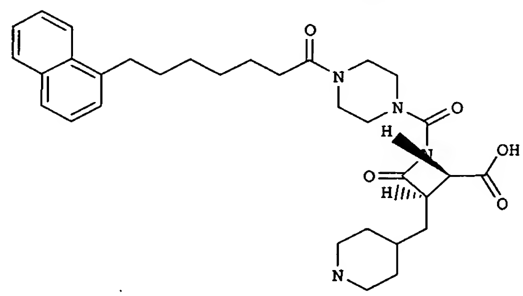
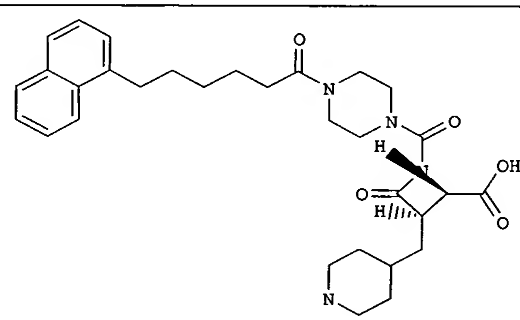
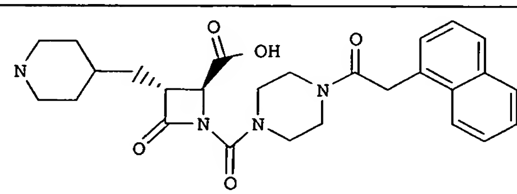
19

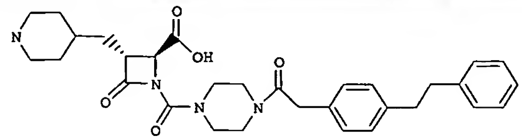
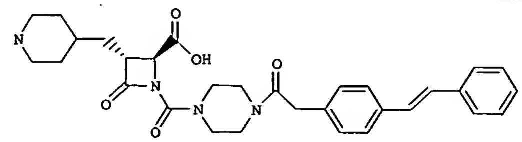
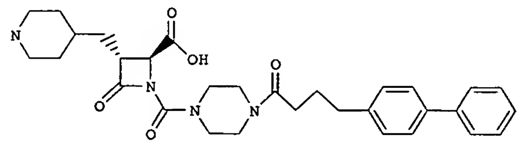
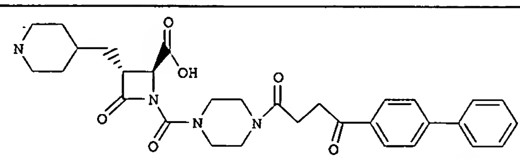
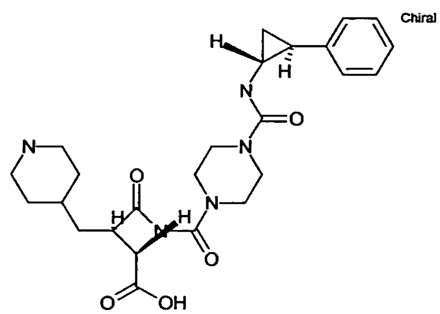
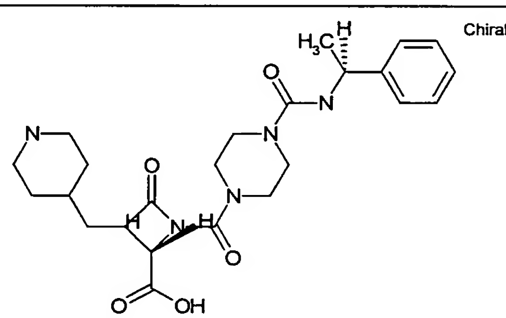
To 3-chlorobenzo[B]thiophene-2-carboxylic acid (0.072 mmol) was added a solution of HOAT in DMA (0.5 ml, 0.12 mmol HOAT in 0.5 ml DMA). After sonicating to dissolve all materials, a solution of DIC in DCM (0.5 ml, 0.12 mmol DIC in 0.5 ml DCM). After agitating the reaction mixture for 1 minute, the reaction mixture was then transferred to a reacting vessel containing Part D compound resin (35 mg). The reaction was aggitated for 36 hours at room temperature. The resin was washed with DMF:DMSO (1:1, 4x5 ml) and DCM (4x5 ml). The resin was then treated with 20% TFA/DCM (1.2 ml) for 2 hours. Eluent was collected and solvent reduced to provide product (14.1 mg); 90% purity by LCMS, (M+H)+ = 519.22.

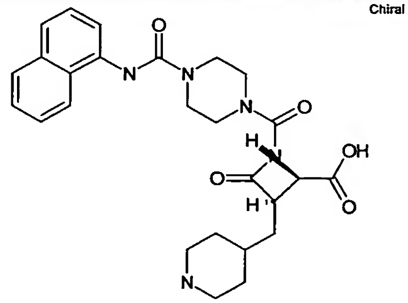
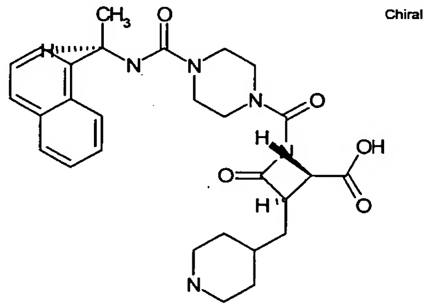
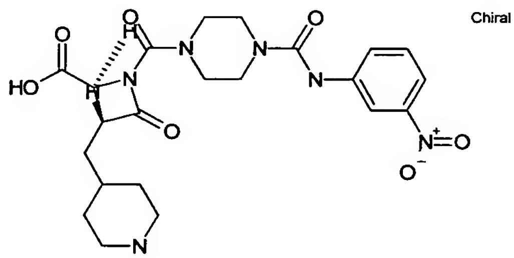
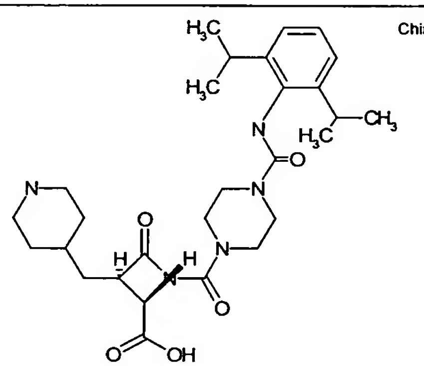
Following the procedures set out in Examples 18 and 19 and in the reaction schemes, the following compounds were prepared:

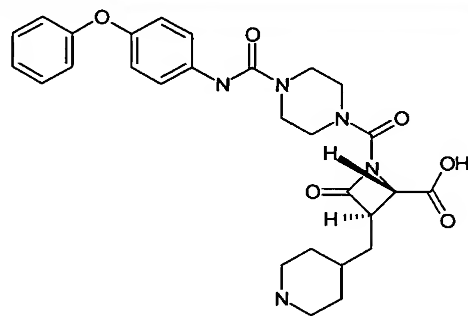
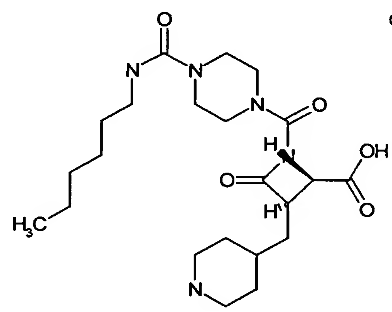
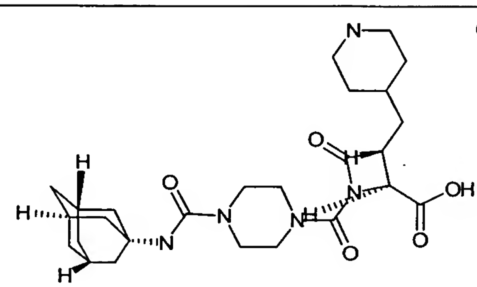
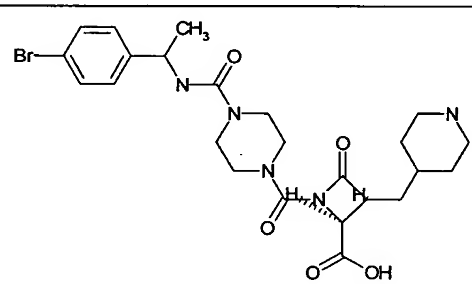
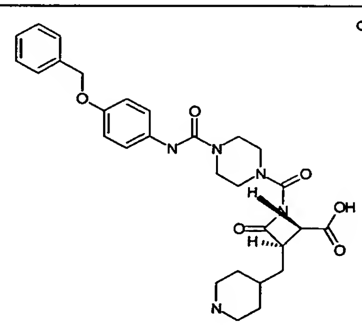
The following additional compounds were prepared following the procedures set out in the Examples and reaction schemes.

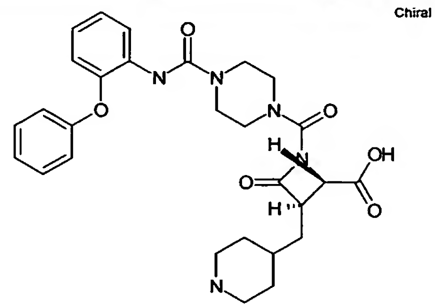
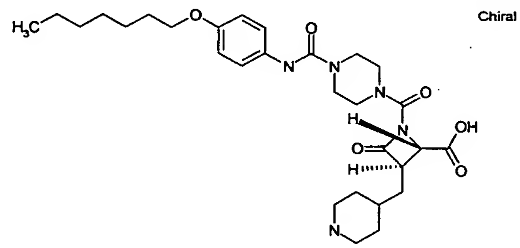
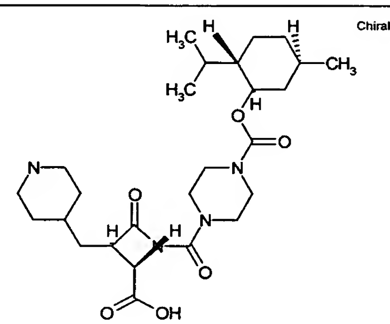
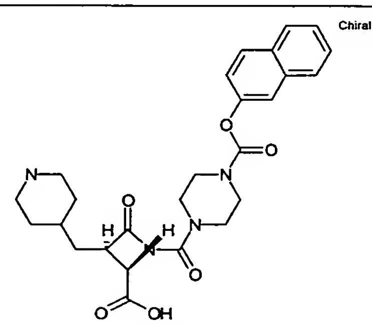
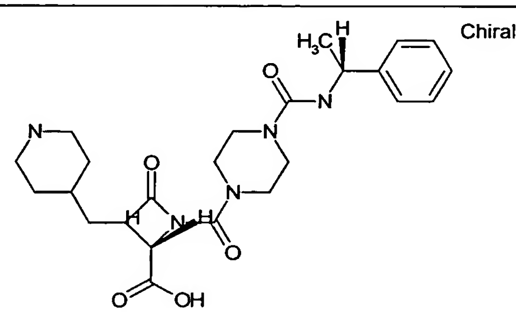
EXAMPLES 20 TO 131

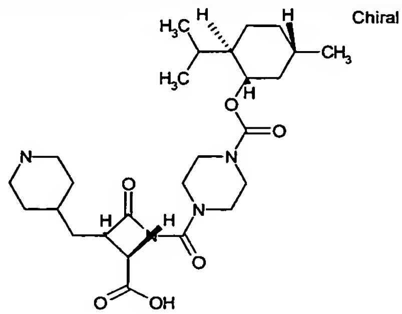
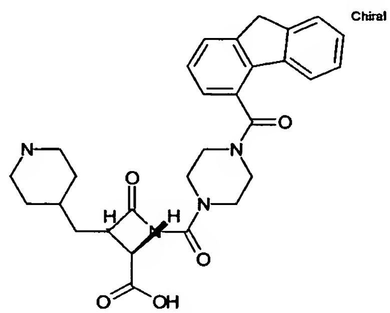
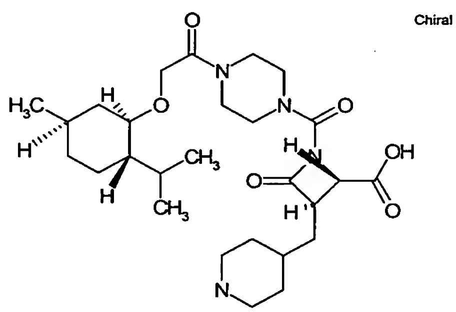
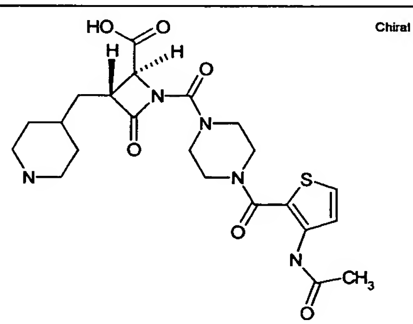
Example No.	Structure	Molecular Weight	(M + H) + observed
20		562.72	563.43
21		548.69	549.40
22		562.72	563.43
23		548.69	549.39
24		492.58	493.32

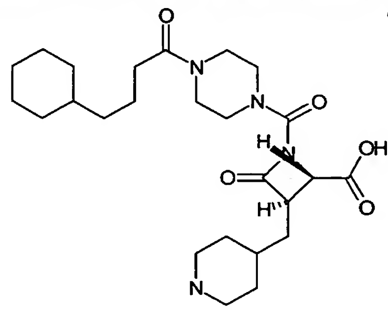
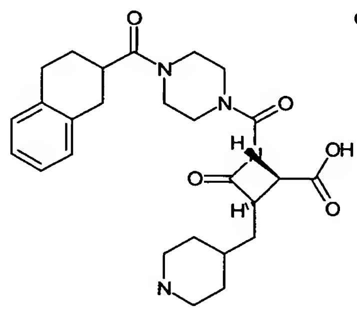
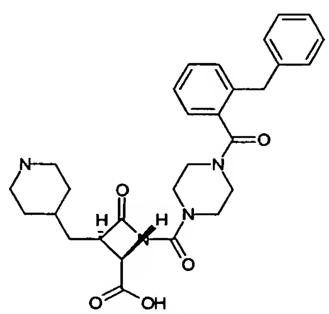
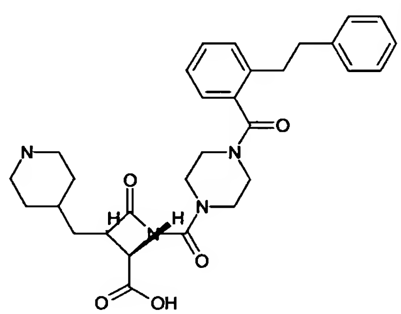
Example No.	Structure	Molecular Weight	(M + H) + observed
25		546.67	547.43
26		544.86	545.29
27		546.67	547.42
28		560.66	561.44
28A		483.566	484.3
29		471.555	472.36

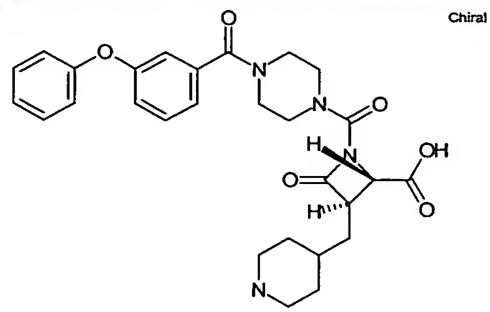
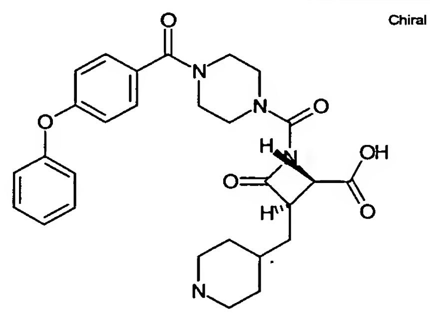
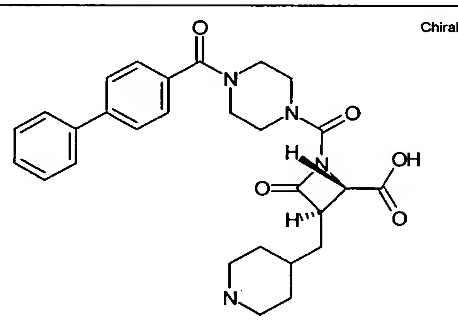
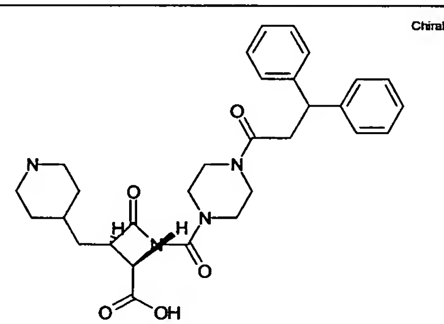
Example No.	Structure	Molecular Weight	(M + H) + observed
30		493.561	494.34
31		521.615	522.37
32		488.498	489.35
33		527.662	528.4

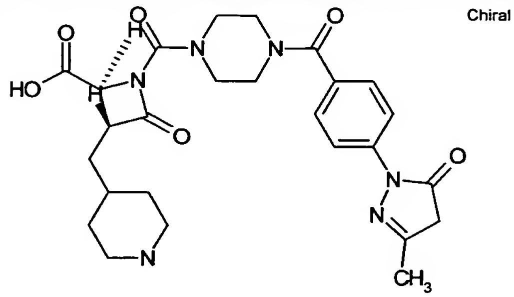
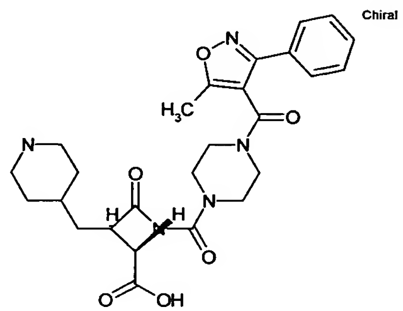
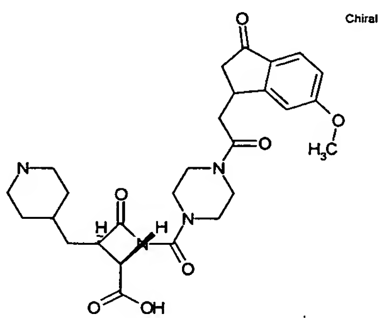
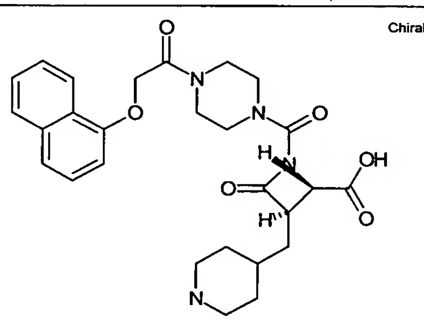
Example No.	Structure	Molecular Weight	(M + H) + observed
34	 Chiral	535.598	536.32
35	 Chiral	451.564	452.38
36	 Chiral	501.624	502.37
37	 Chiral	550.451	550.25, 552.24
38	 Chiral	549.625	550.37

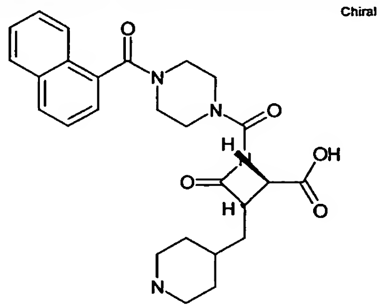
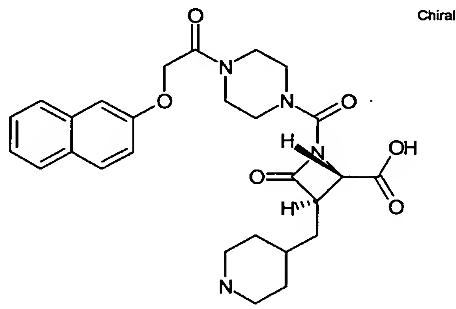
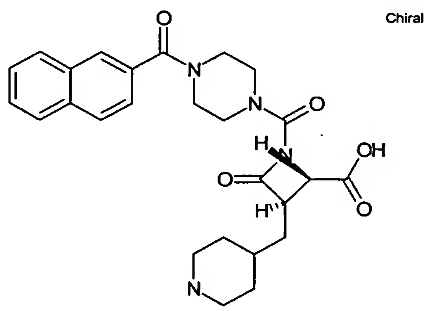
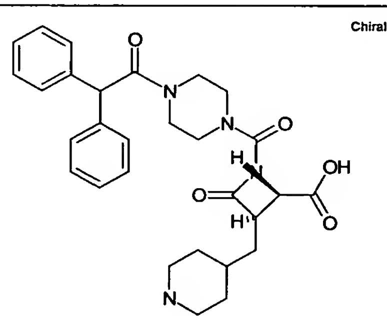
Example No.	Structure	Molecular Weight	(M + H) + observed
39		535.598	536.33
40		557.688	558.42
41		506.64	507.4
42		494.545	495.26
43		471.555	472.36

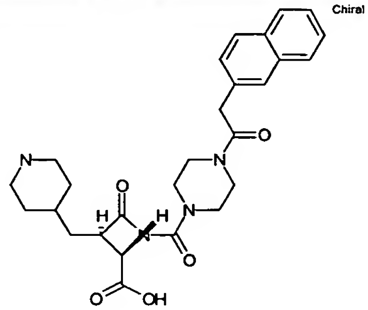
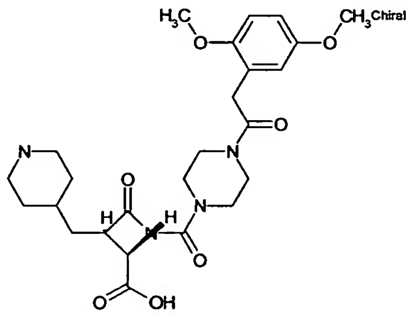
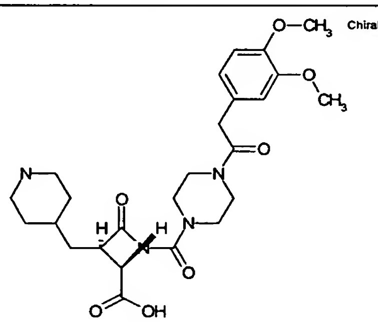
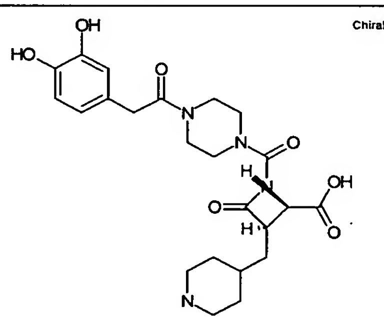
Example No.	Structure	Molecular Weight	(M + H) + observed
44		506.64	507.35
45		516.595	517.26
46		520.667	521.35
47		491.566	492.25

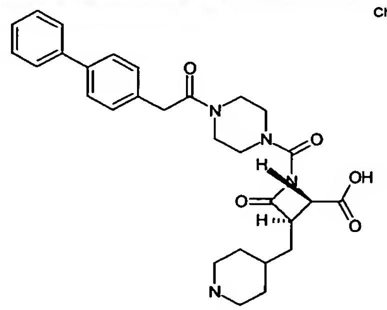
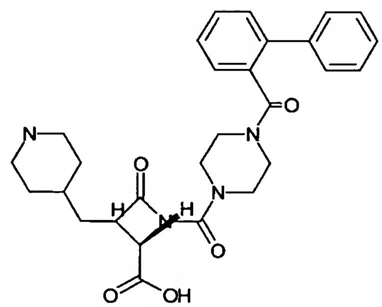
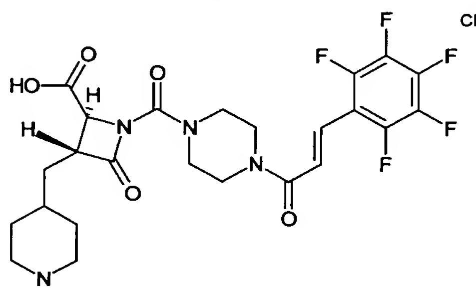
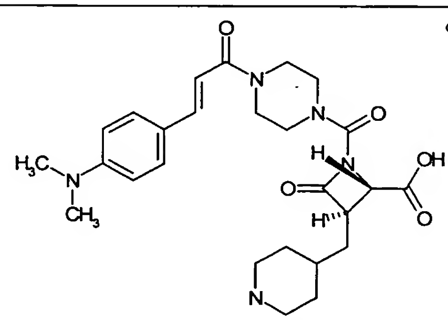
Example No.	Structure	Molecular Weight	(M + H) + observed
48		476.614	477.37
49		482.578	483.32
50		518.611	519.27
51		532.637	533.31

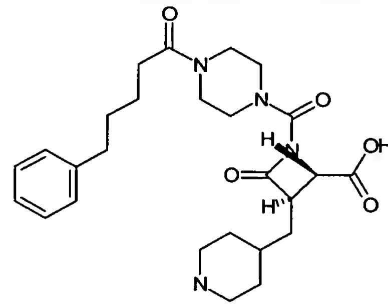
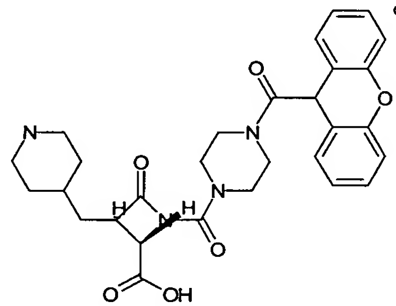
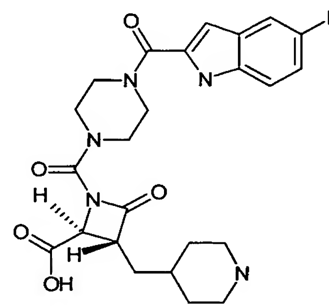
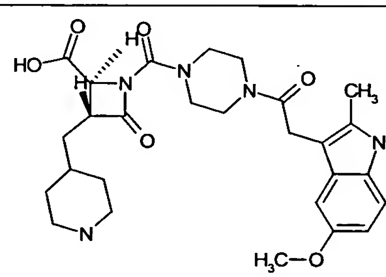
Example No.	Structure	Molecular Weight	(M + H) + observed
52		520.583	521.25
53		520.583	521.25
54		504.584	505.27
55		532.637	533.31

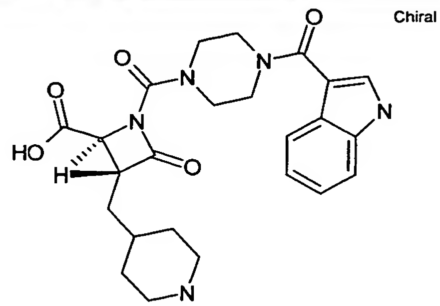
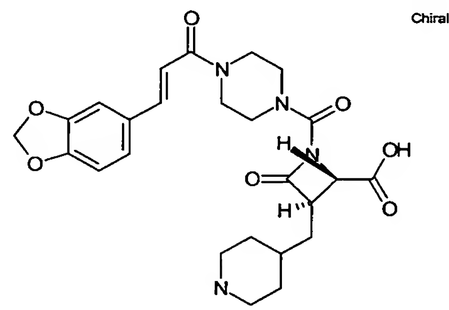
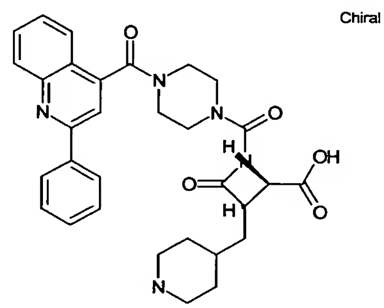
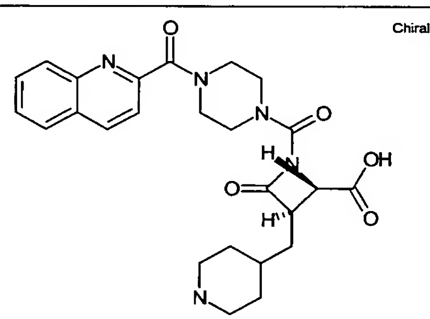
Example No.	Structure	Molecular Weight	(M + H) + observed
56		524.575	525.32
57		509.56	510.25
58		526.587	527.27
59		580.572	509.24

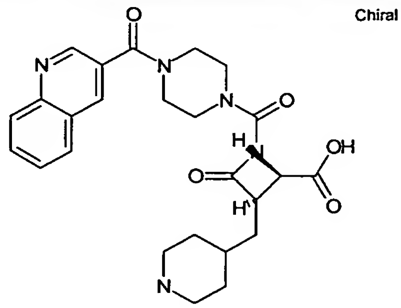
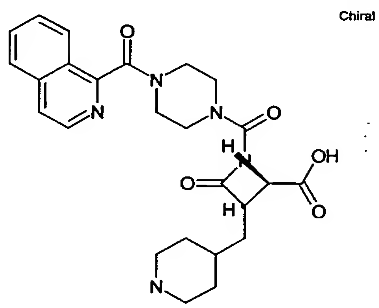
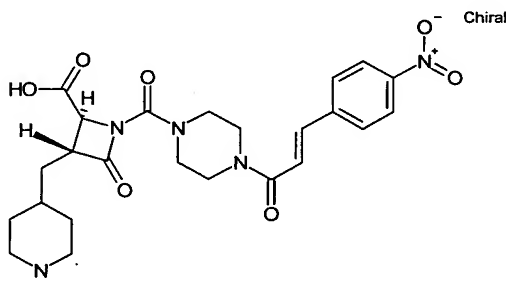
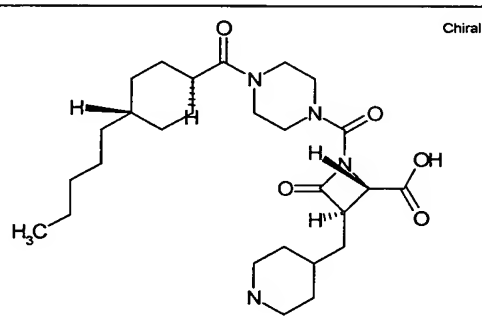
Example No.	Structure	Molecular Weight	(M + H) + observed
60		478.546	479.29
61		508.572	509.25
62		478.546	479.31
63		518.611	519.27

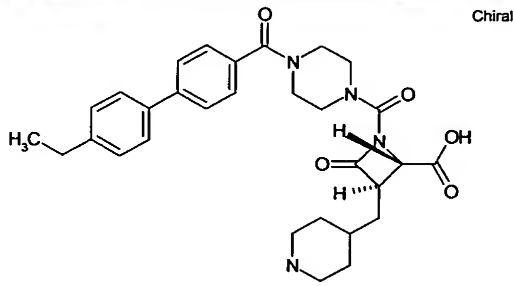
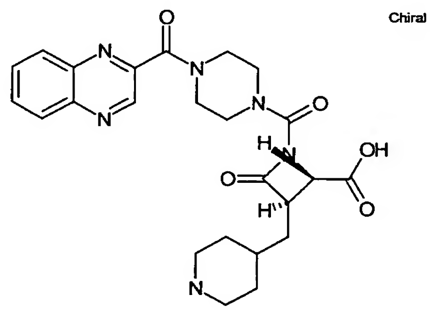
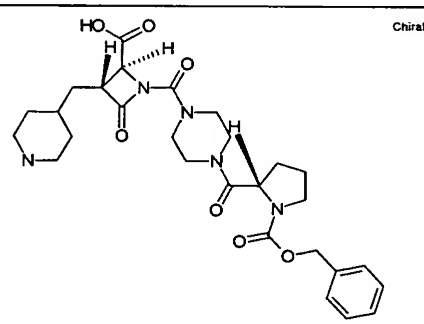
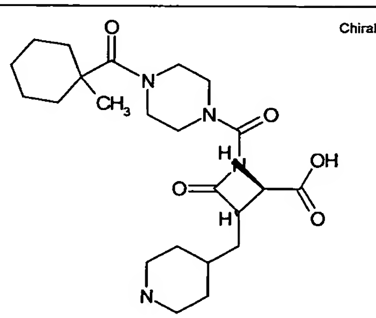
Example No.	Structure	Molecular Weight	(M + H) + observed
64		492.573	493.28
65		502.565	503.28
66		502.565	50.328
67		474.511	475.3

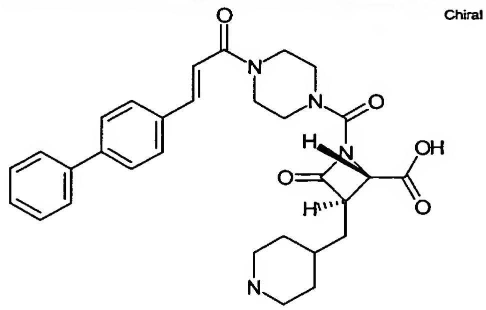
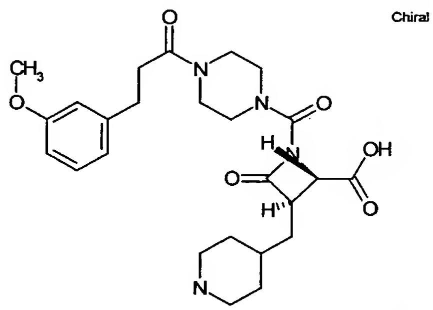
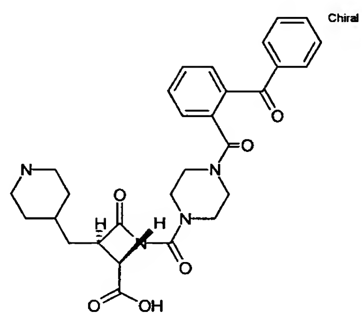
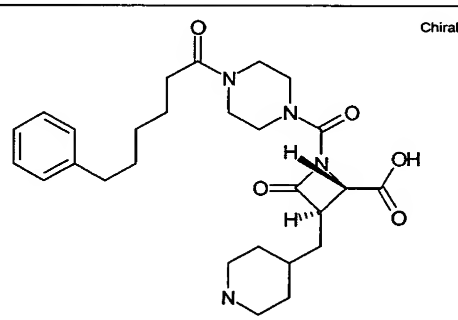
Example No.	Structure	Molecular Weight	(M + H) + observed
68		518.611	519.27
69		504.584	505.27
70		544.474	545.25
71		497.592	498.33

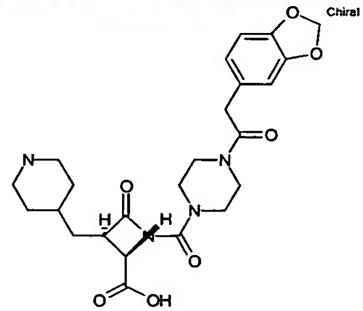
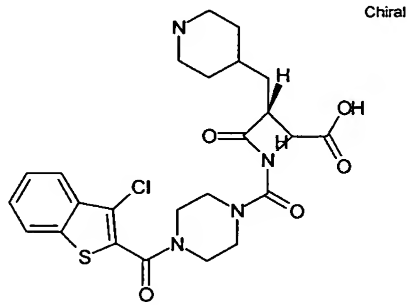
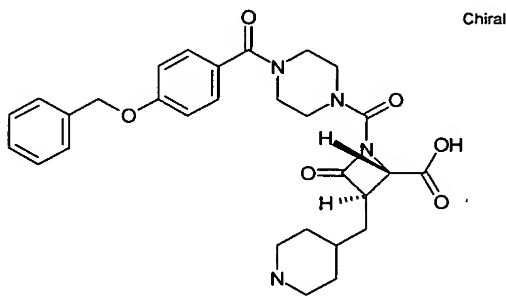
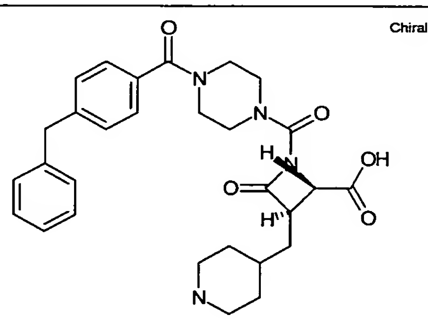
Example No.	Structure	Molecular Weight	(M + H) + observed
72		484.593	485.33
73		532.594	533.27
74		485.513	486.29
75		525.602	526.33

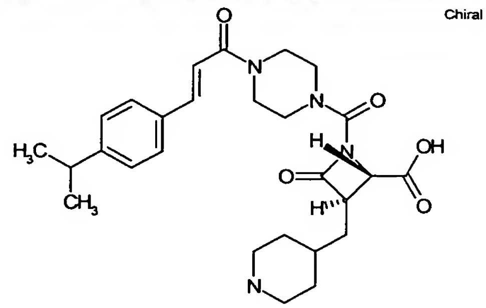
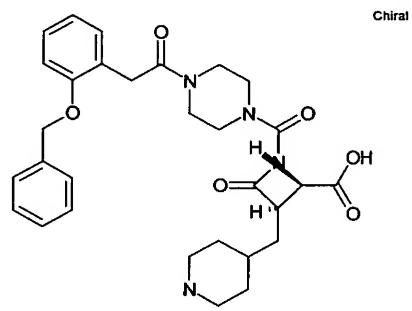
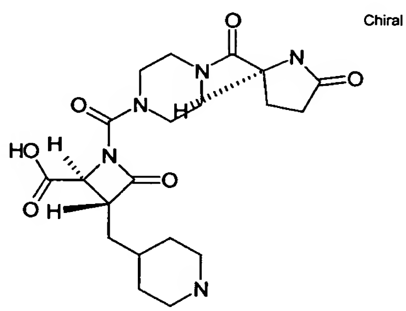
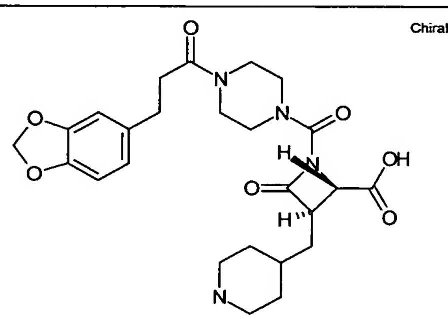
Example No.	Structure	Molecular Weight	(M + H) + observed
76		467.523	468.3
77		498.533	499.25
78		555.632	556.33
79		479.534	480.29

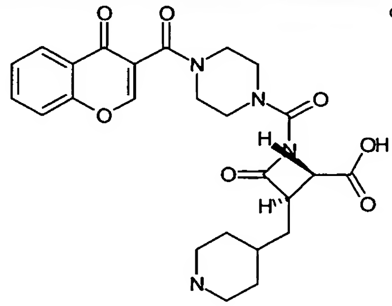
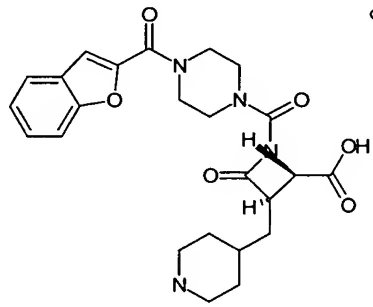
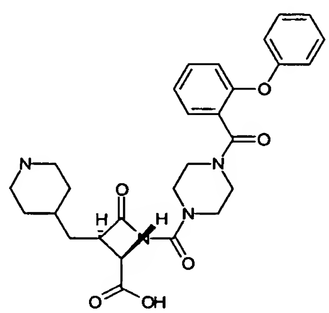
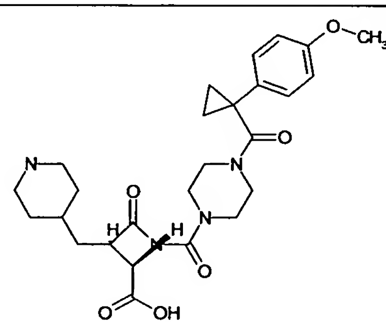
Example No.	Structure	Molecular Weight	(M + H) + observed
80		479.534	480.31
81		479.534	480.28
82		499.521	500.3
83		504.668	505.37

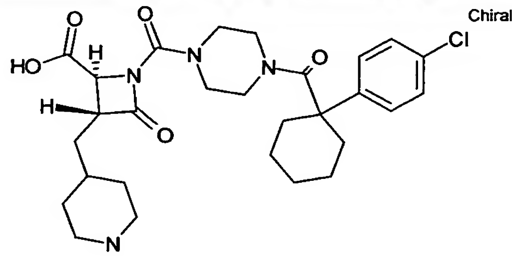
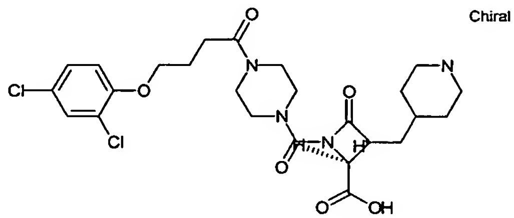
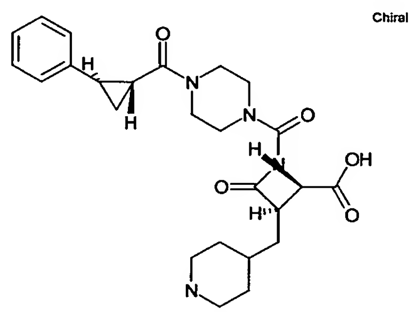
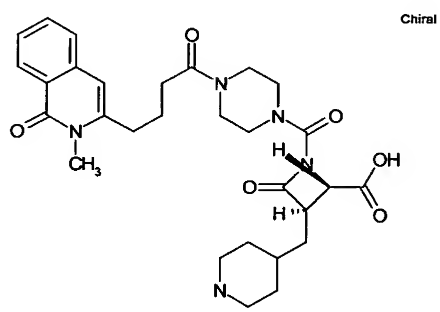
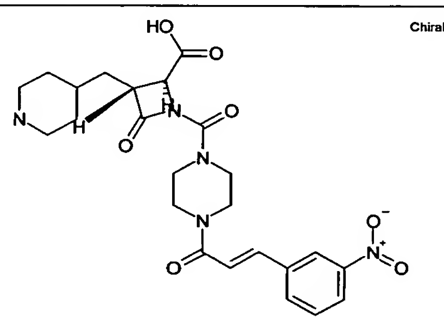
Example No.	Structure	Molecular Weight	(M + H) + observed
84		532.637	533.31
85		480.522	481.27
86		555.628	556.34
87		448.56	449.33

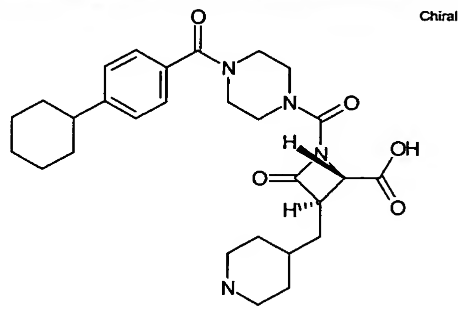
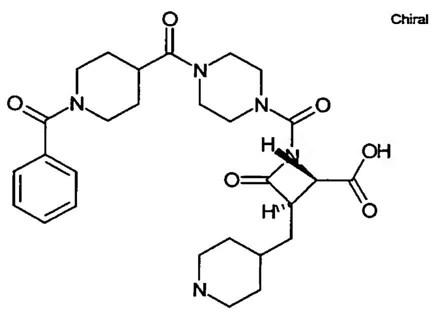
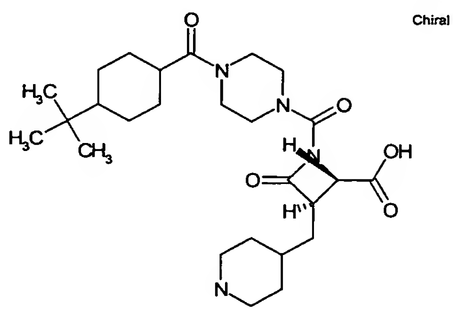
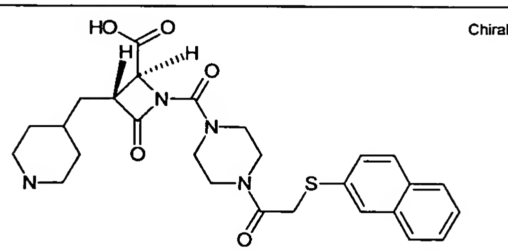
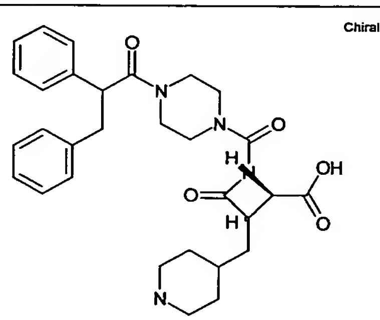
Example No.	Structure	Molecular Weight	(M + H) + observed
88		530.622	531.33
89		486.566	487.33
90		532.594	533.32
91		498.62	499.38

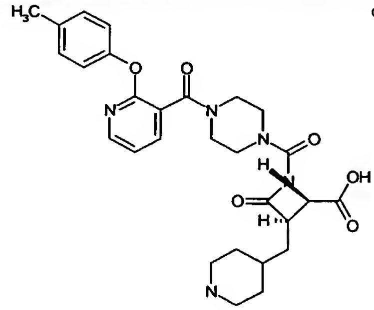
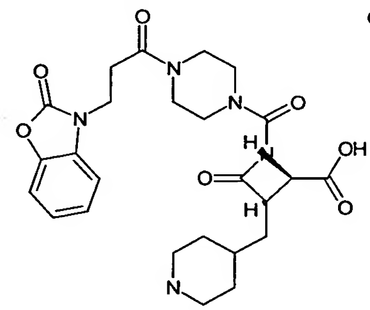
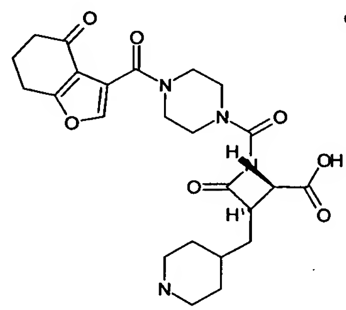
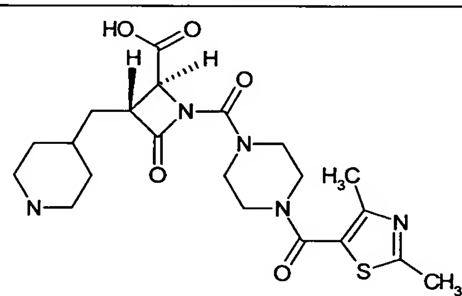
Example No.	Structure	Molecular Weight	(M + H) + observed
92		486.522	487.3
93		519.019	519.22
94		534.61	535.33
95		518.611	519.33

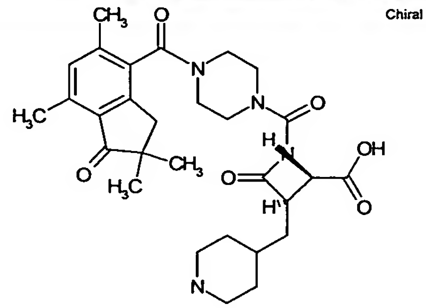
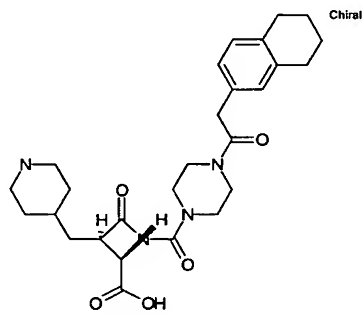
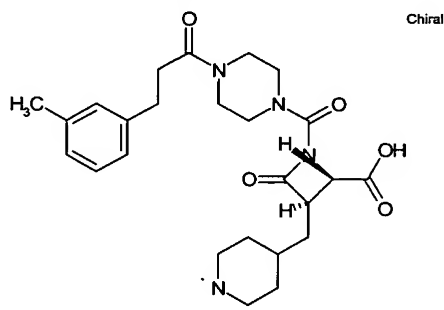
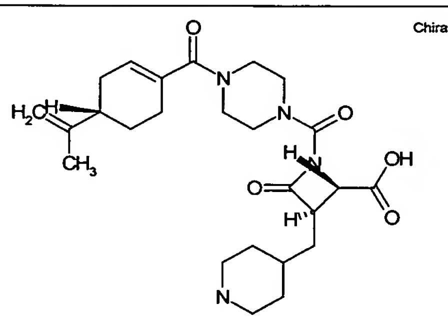
Example No.	Structure	Molecular Weight	(M + H) + observed
96		496.604	497.36
97		548.636	549.37
98		435.478	436.3
99		500.549	501.32

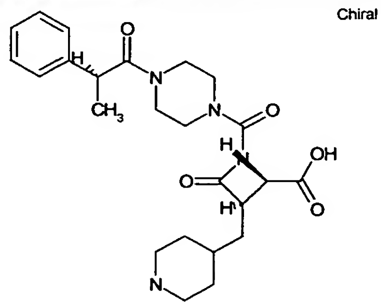
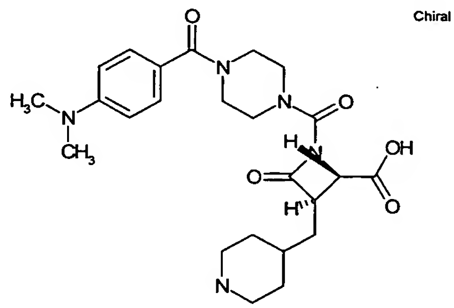
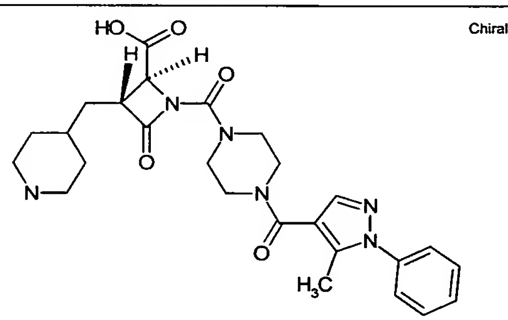
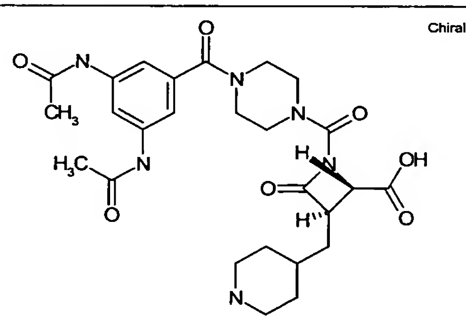
Example No.	Structure	Molecular Weight	(M + H) + observed
100		496.517	497.29
101		468.507	469.33
102		520.583	521.32
103		498.577	499.33

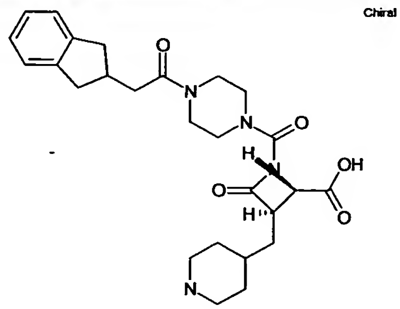
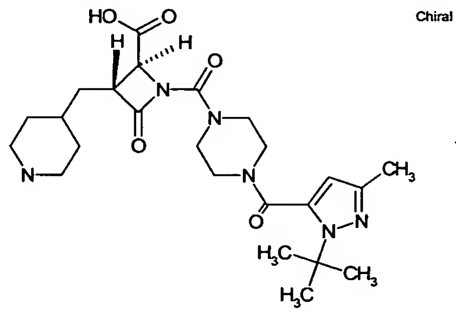
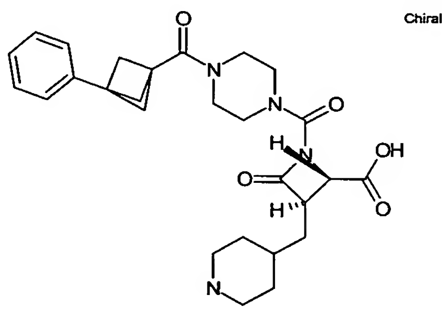
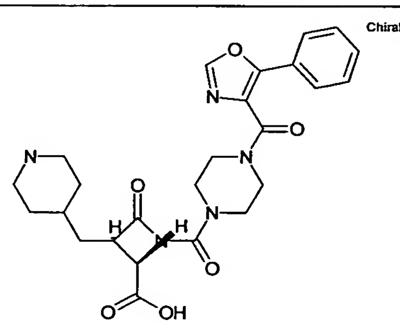
Example No.	Structure	Molecular Weight	(M + H) + observed
104		545.076	545.34
105		555.456	555.27
106		468.551	469.37
107		551.64	552.38
108		499.521	500.29

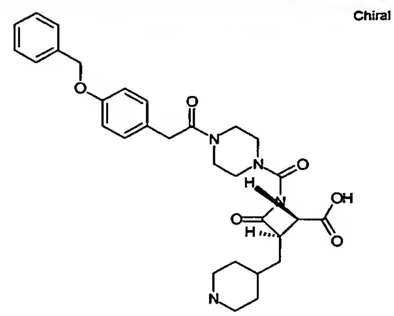
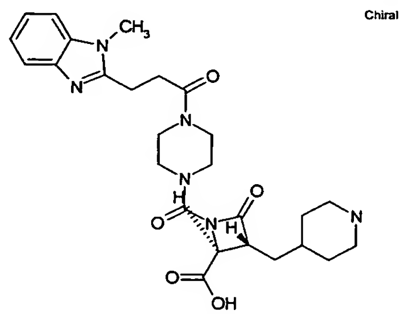
Example No.	Structure	Molecular Weight	(M + H) + observed
109		510.631	511.36
110		539.629	540.37
111		490.641	491.42
112		524.639	525.29
113		532.637	533.36

Example No.	Structure	Molecular Weight	(M + H) + observed
114		535.598	536.34
115		513.548	514.3
116		486.522	487.3
117		463.556	464.32

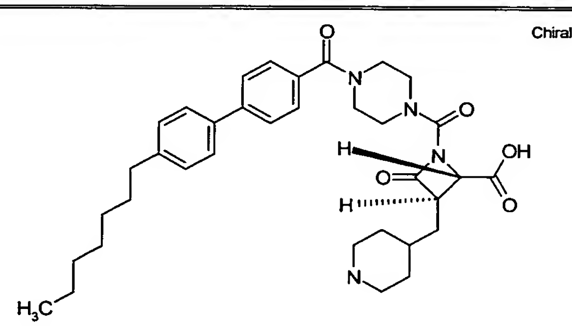
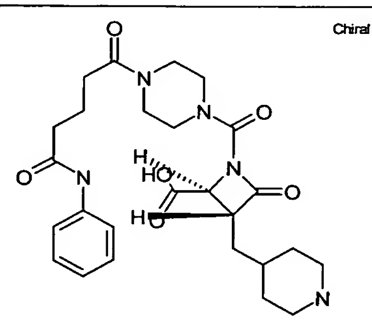
Example No.	Structure	Molecular Weight	(M + H) + observed
118		538.641	539.37
119		496.604	497.36
120		470.567	471.36
121		472.582	473.34

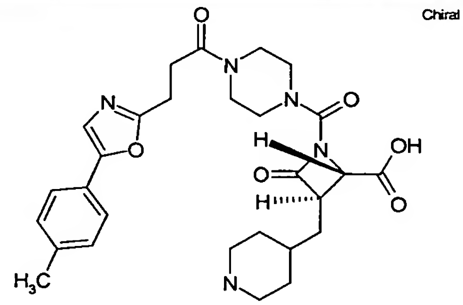
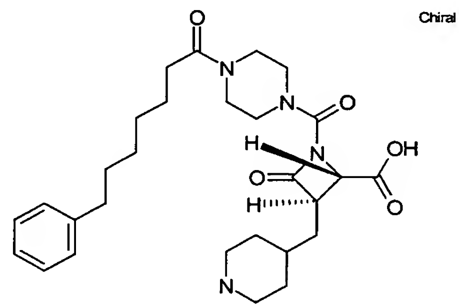
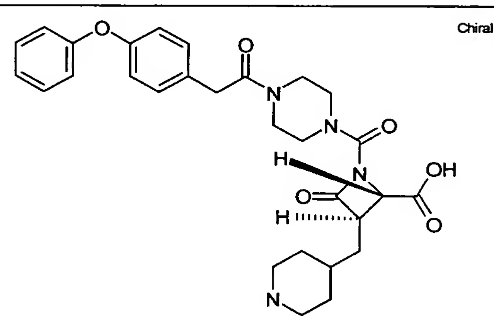
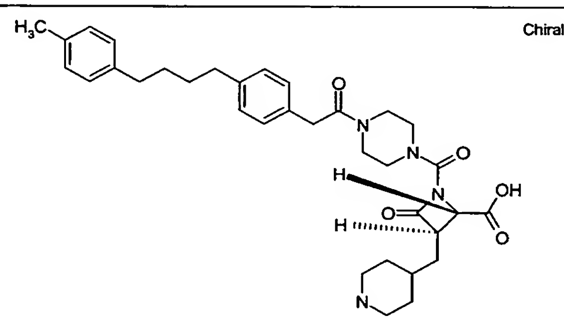
Example No.	Structure	Molecular Weight	(M + H) + observed
122		456.54	457.34
123		471.555	473.35
124		508.576	509.32
125		542.59	543.35

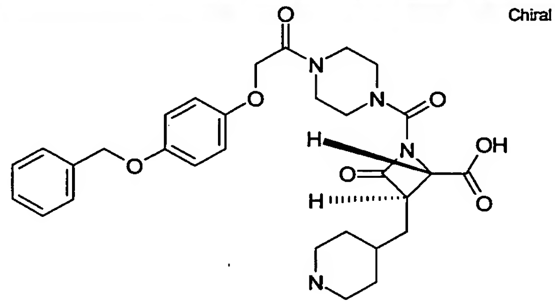
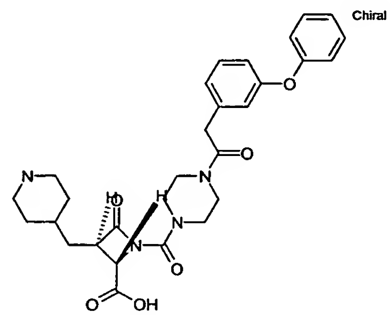
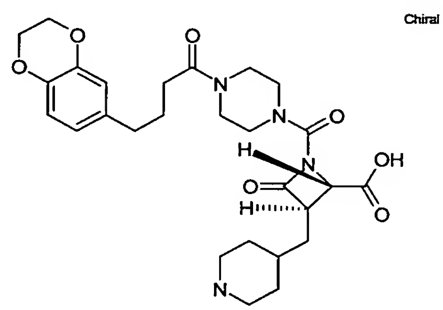
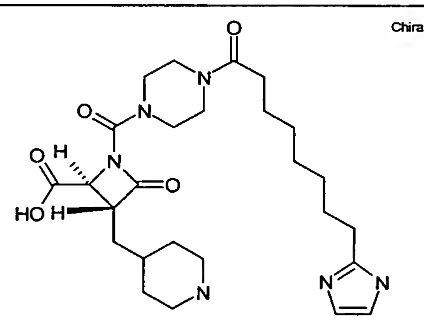
Example No.	Structure	Molecular Weight	(M + H) + observed
126		482.578	483.37
127		488.585	489.38
128		494.589	495.35
129		495.533	496.32

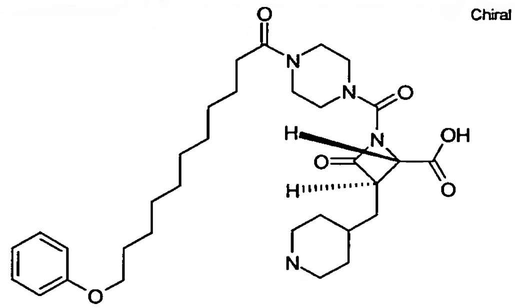
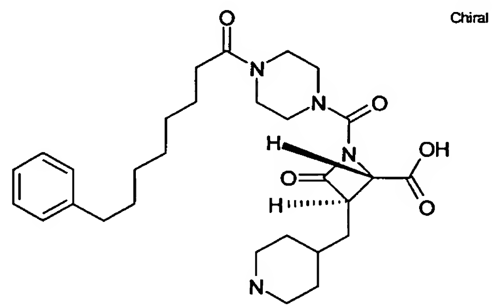
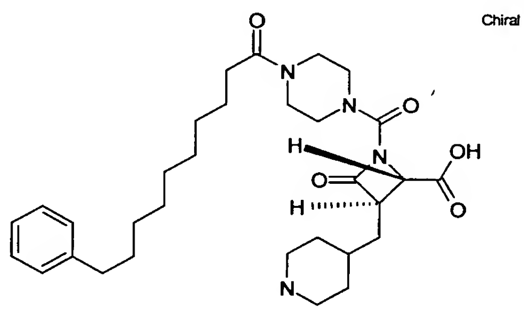
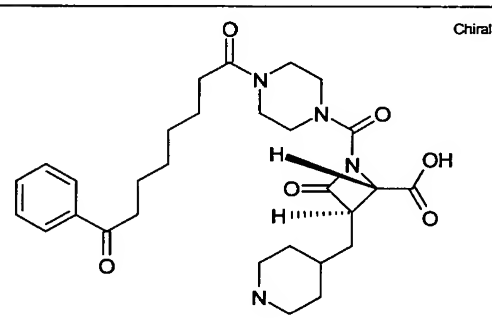
Example No.	Structure	Molecular Weight	(M + H) + observed
130		548.636	549.38
131		510.592	511.35

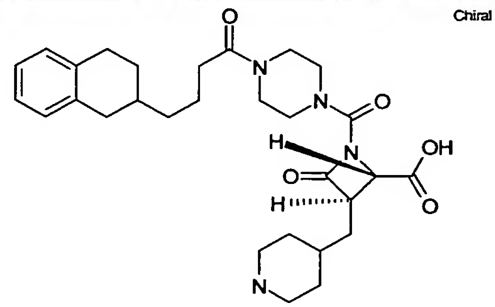
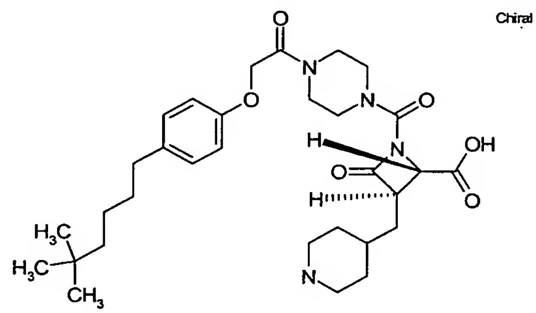
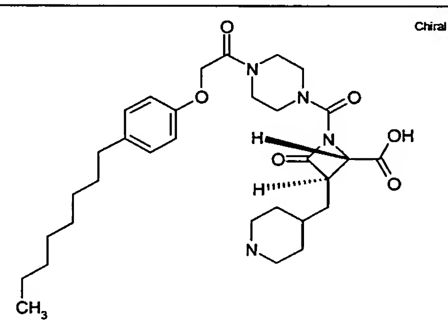
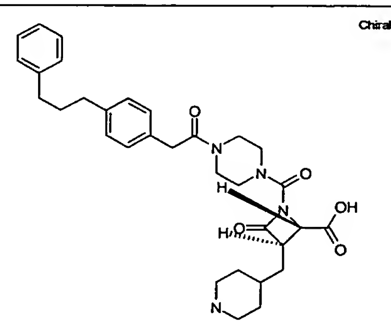
EXAMPLES 132 TO 168

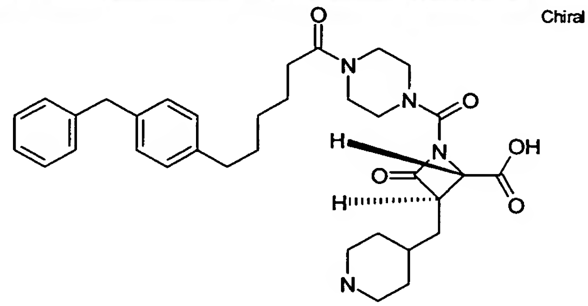
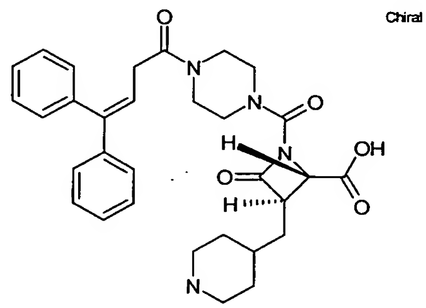
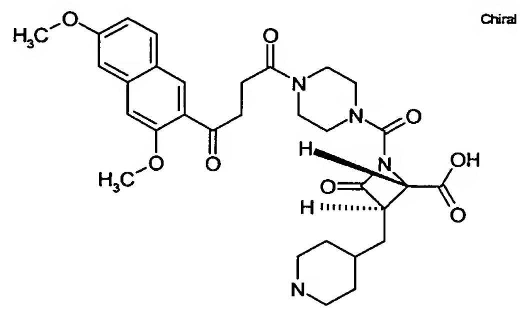
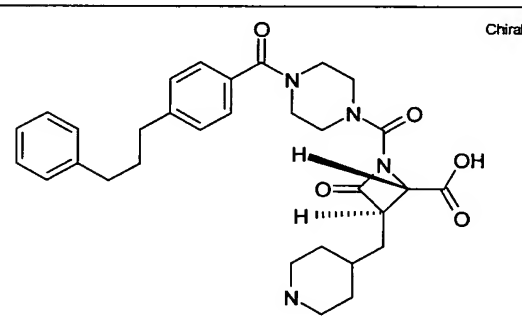
Example No.	Structure
132	
133	

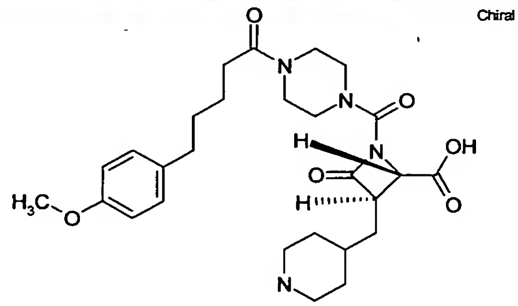
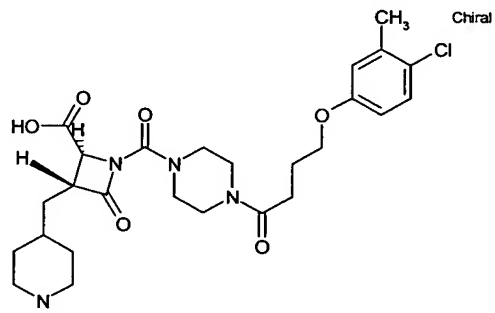
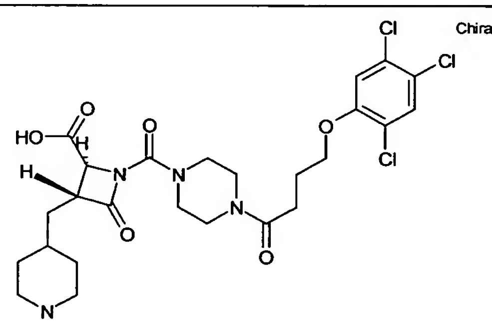
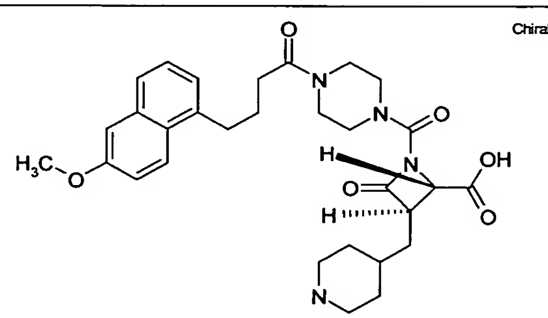
Example No.	Structure
134	
135	
136	
137	

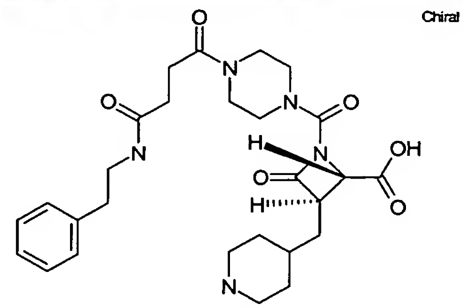
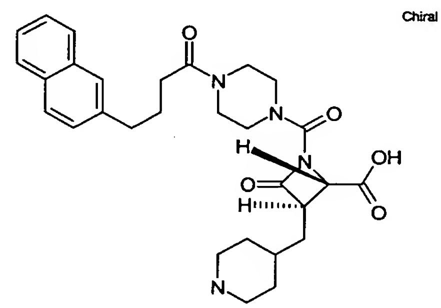
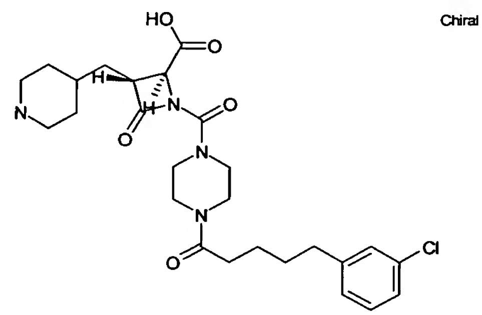
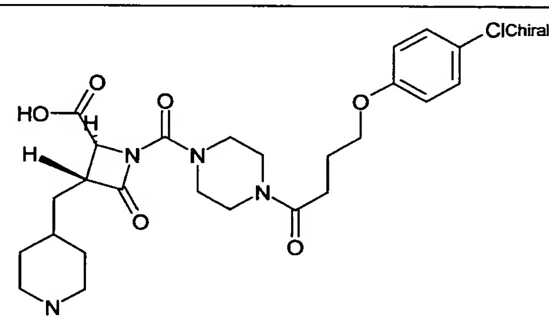
Example No.	Structure
138	
139	
140	
141	

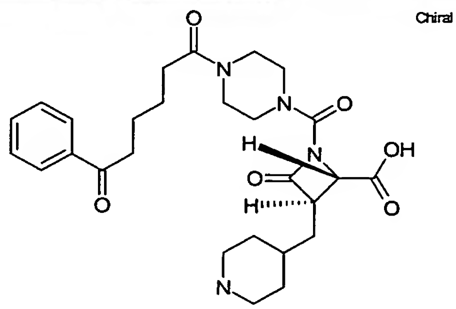
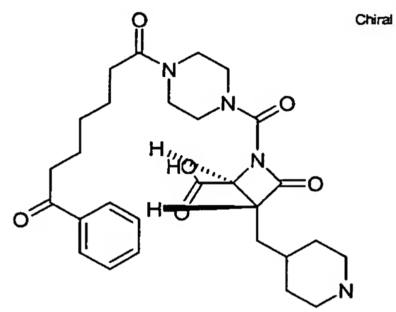
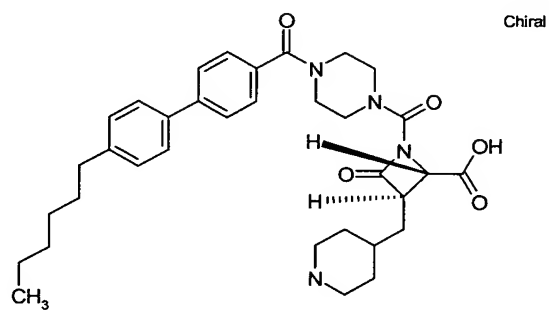
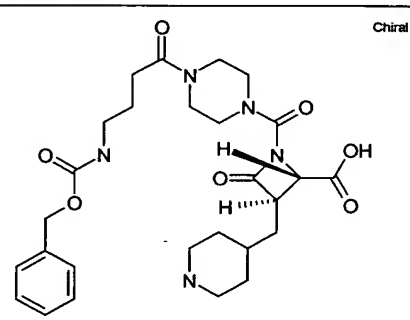
Example No.	Structure
142	
143	
144	
145	

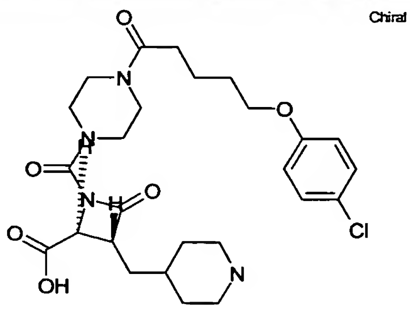
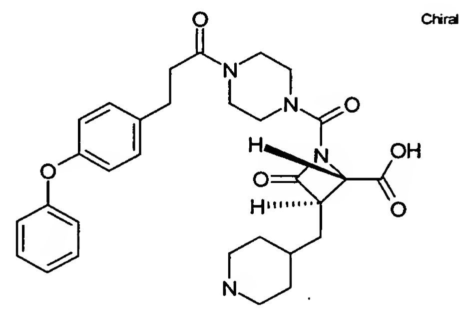
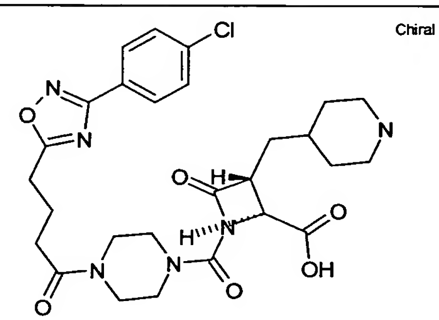
Example No.	Structure
146	
147	
148	
149	

Example No.	Structure
150	
151	
152	
153	

Example No.	Structure
154	
155	
156	
157	

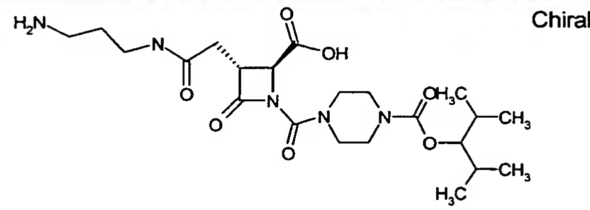
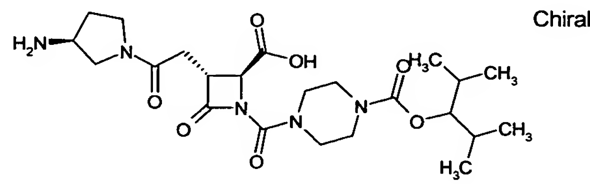
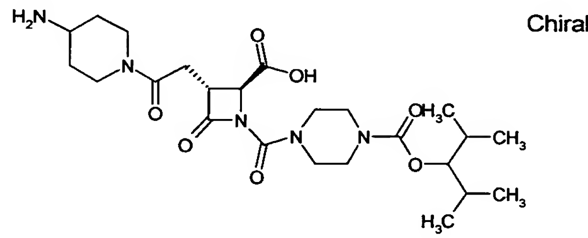
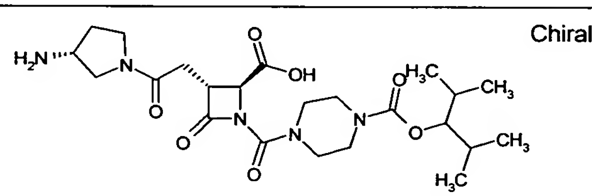
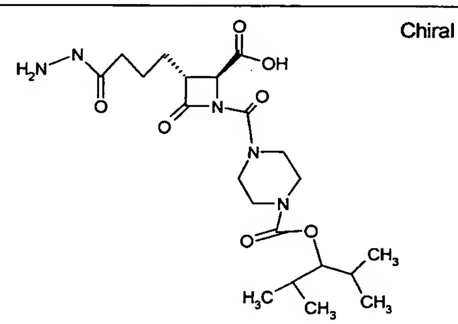
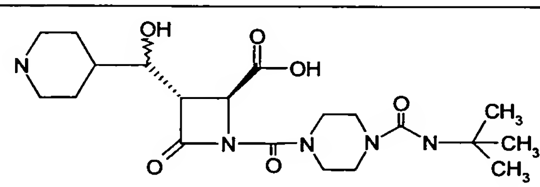
Example No.	Structure
158	
159	
160	
161	

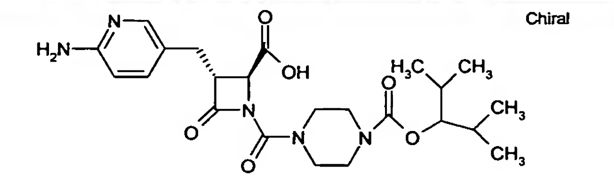
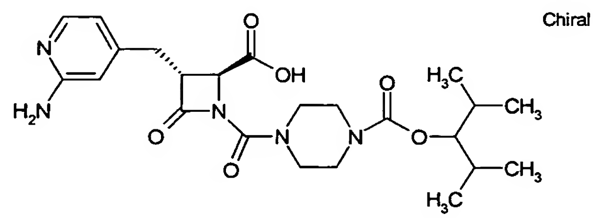
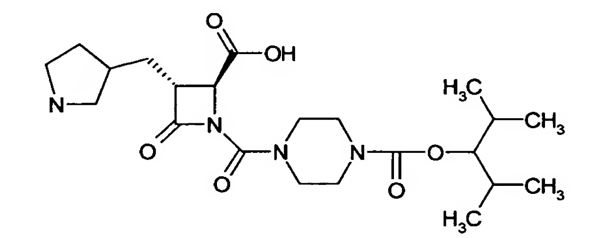
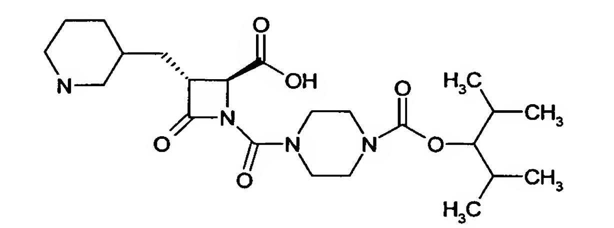
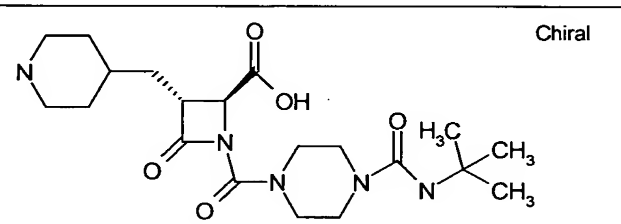
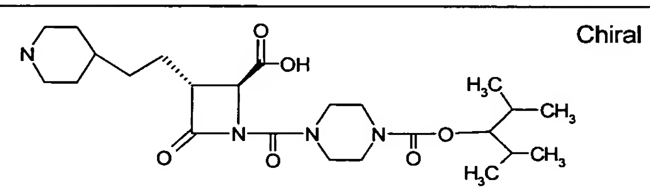
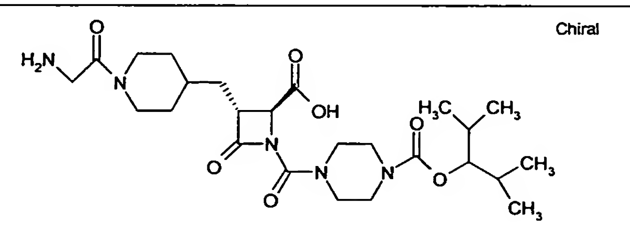
Example No.	Structure
162	
163	
164	
165	

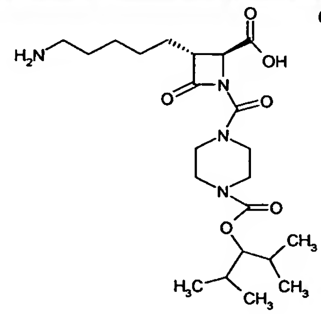
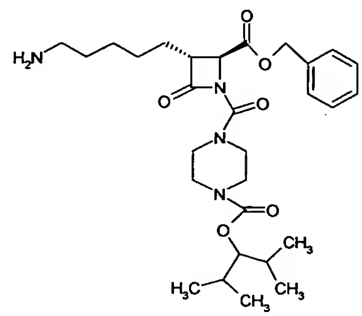
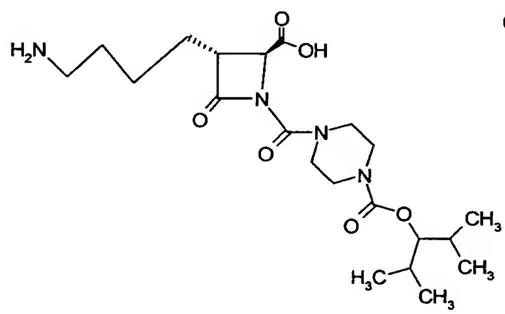
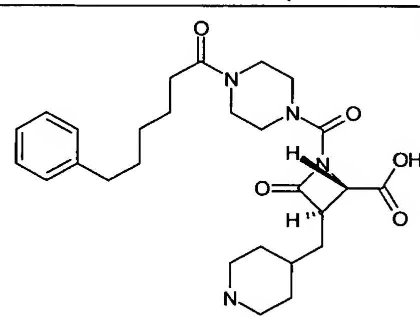
Example No.	Structure
166	
167	
168	

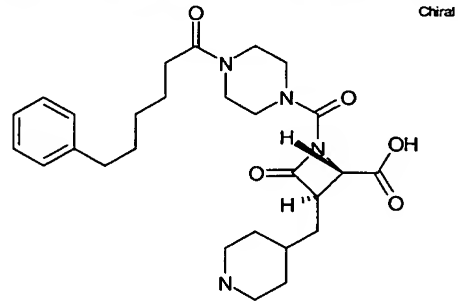
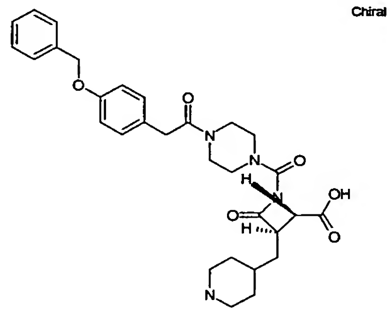
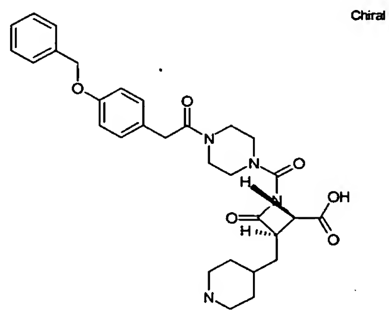
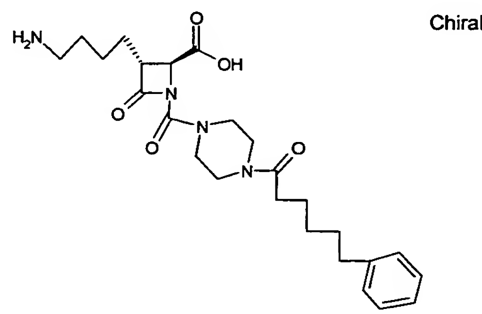
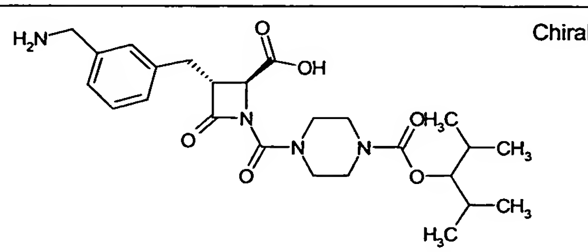
The following additional Examples were prepared employing procedures set out hereinbefore in the reaction schemes and working Examples.

EXAMPLES 169 TO 191

Example No.	Structure
169	
170	
171	
172	
173	
174	

Example No.	Structure
175	
176	
177	
178	
179	
180	
181	

Example No.	Structure
182	
183	
184	
185	

Example No.	Structure
186	
187	
188	
189	
190	

Example No.	Structure
191